JC20 Rec'd PCT/PTO 27 FEB 2002

U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		TAKAYAMA10
		U.S. APPLICATION NO (If known,see 37 CFR 1 5) 10/069481
INTERNATIONAL APPLICATION NO. PCT/JP00/05743	INTERNATIONAL FILING DATE 25 AUGUST 2000	PRIORITY CLAIMED 27 AUGUST 1999
TITLE OF INVENTION 2α-SUBSTITUTED VITAMIN D DERIVATIVES		
APPLICANT(S) FOR DO/EO/US **Hiroaki TAKAYAMA et al.**		

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [xx] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [xx] This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [xx] The US has been elected in a Demand by the expiration of 19 months from the priority date (PCT Article 31).
5. [xx] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [ ] is attached hereto (required only if not transmitted by the International Bureau).
   b. [xx] has been communicated by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US).
6. [xx] An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
7. [xx] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been communicated by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [xx] have not been made and will not be made.
8. [ ] An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [xx] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. [ ] An English language translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An Assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [xx] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [xx] Other items or information:
    [xx] Courtesy copy of the first page of the International Publication (WO 01/16099).
    [xx] Courtesy copy of the International Preliminary Examination Report. There were no annexes
    [ ] Formal drawings, ____ sheets, Figures ____.
    [xx] Courtesy Copy of the International Search Report.
    [xx] The application is (or will be) assigned to:CHUGAI SEIYAKU KABUSHIKI KAISHA, whose address is 5-1, Ukima 5-chome, Kita-ku, Tokyo 115-8543 Japan.

U.S. APPLICATION NO. (If known, see 37 CFR 1.5)	International Application No.	Attorney's Docket No.
10/069481	PCT/JP00/05743	TAKAYAMA10

17. [xx] The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a)(1) –(5):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO.....**$1040.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO.....**$890.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO.....**$740.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4).....**$710.00**

International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4).....**$100.00**

	CALCULATIONS PTO USE ONLY
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$

Claims as Originally Presented	Number Filed	Number Extra	Rate	
Total Claims	- 40	20	X $18.00	$ 360.00
Independent Claims	- 3	0	X $84.00	$
Multiple Dependent Claims (if applicable)			+$280.00	$ 280.00
TOTAL OF ABOVE CALCULATIONS =				$1,530.00

Claims After Post Filing Prel. Amend	Number Filed	Number Extra	Rate	
Total Claims	- 20		X $18.00	$
Independent Claims	- 3		X $84.00	$
TOTAL OF ABOVE CALCULATIONS =				$1,530.00
Reduction of ½ for filing by small entity, if applicable. Applicant claims small entity status. See 37 CFR 1.27.				$
SUBTOTAL =				$1,530.00
Processing fee of **$130.00** for furnishing the English translation later than [ ]20 [ ]30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$
TOTAL NATIONAL FEE =				$1,530.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). **$40.00** per property +				$
TOTAL FEES ENCLOSED =				$1,530.00
			Amount to be: refunded	$
			charged	$

a. [ ] A check in the amount of $_____ to cover the above fees is enclosed.

b. [xx] Credit Card Payment Form (PTO-2038), authorizing payment in the amount of $ 1,530.00, is attached.

c. [ ] Please charge my Deposit Account No. **02-4035** in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

d. **[XX]** The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. **02-4035**. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

BROWDY AND NEIMARK, P.L.L.C.
624 NINTH STREET, N.W., SUITE 300
WASHINGTON, D.C. 20001
TEL: (202) 628-5197
FAX: (202) 737-3528

Date of this submission: **February 27, 2002**

SIGNATURE

Roger L. Browdy

NAME

25,618

REGISTRATION NUMBER

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 5 and 7 have been amended as follows:

5 (Amended). The vitamin D derivative according to one of claims 1 to 43, wherein R^1 is a 4-hydroxy-4-methylpentyl group.

7 (Amended). A pharmaceutical composition comprising a vitamin D derivative according to any one of claims 1, 2, 3 ~~to~~ or 6 as an active ingredient.

New claims 9-15 have been added.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

ATTY DOCKET: TAKAYAMA=10

In re Application of:

Hiroaki TAKAYAMA et al.

IA No.: PCT/JP00/05743

IA Filed: 25 August 2000

U.S. App. No.:
(Not Yet Assigned)

National Filing Date:
(Not Yet Received)

For: 2α-SUBSTITUTED VITAMIN D DERIVATIVES

Art Unit:

Washington, D.C.

February 27, 2002

PRELIMINARY AMENDMENT

Honorable Commissioner for Patents and Trademarks
Washington, D.C. 20231

Sir:

Prior to examination on the merits, kindly amend as follows:

IN THE CLAIMS

Please rewrite claims 5 and 7 in amended form as follows:

5 (Amended). The vitamin D derivative according to one of claims 1 to 3, wherein R^1 is a 4-hydroxy-4-methylpentyl group.

7 (Amended). A pharmaceutical composition comprising a vitamin D derivative according to any one of claims 1, 2, 3 or 6 as an active ingredient.

Please add new claims 9- as follows:

9 (New). The vitamin D derivative according to claim 4, wherein R^1 is a 4-hydroxy-4-methylpentyl group.

10 (New). A pharmaceutical composition comprising a vitamin D derivative according to claim 4 as an active ingredient.

11 (New). A pharmaceutical composition comprising a vitamin D derivative according to claim 5 as an active ingredient.

12 (New). A pharmaceutical composition comprising a vitamin D derivative according to claim 9 as an active ingredient.

13 (New). The pharmaceutical composition according to claim 10, wherein the composition is a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

14 (New). The pharmaceutical composition according to claim 11, wherein the composition is a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

15 (New). The pharmaceutical composition according to claim 12, wherein the composition is a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

In re of: National Stage of PCT/JP00/05743

REMARKS

Claims 1-15 presently appear in this application. The present amendments have been made to place the case in better condition for examination.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made**."

Favorable consideration and allowance are earnestly solicited.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By [signature]
Roger L. Browdy
Registration No.

RLB:rd
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
F:\,Y\YUAS\Takayama10\PTO\Preliminary Amendment.doc

SPECIFICATION

2α-SUBSTITUTED VITAMIN D DERIVATIVES

TECHNICAL FIELD

The present invention relates to novel vitamin D derivatives, more particularly, relates to vitamin D derivatives having a substituent at the 2α-position.

BACKGROUND ART

Active vitamins D_3 including 1α,25-dihydroxyvitamin D_3 are known to exhibit a variety of physiological activities such as calcium metabolism regulatory activities, growth inhibitory and differentiation toward tumor cells, and immunoregulatory activities. However, some active vitamins D_3 disadvantageously may cause hypercalcemia during long-term and continuous administration, and are thus not suitable for use as antitumor agents, antirheumatic agents, or the like. Thus, a number of synthetic studies have been conducted for the purpose of obtaining vitamin D derivatives which are superior in certain activities.

The studies conducted by the inventors of the present invention revealed that 2α-methylderivatives of active vitamin D_3, i.e., 1α,25-dihydroxyvitamin D_3, increases binding property to vitamin D receptor (VDR) (K.Konno, et al., Bioorg. Med. Chem. Lett., 1998, 8, 151). Furthermore, a combination of the 2α-methylation and epimerization at the 20-position on the side chain has been reported to

additionally enhance the binding property to VDR (T.Fujishima et al., Bioorg. Med. Chem. Lett., 1998, 8, 2145).

However, no work has been done to synthesize a vitamin D derivative, in which the 2-position is substituted, other than with a methyl group, and the groups at the 20-position are epimerized; further, the physiological activities of such a vitamin D derivative have not been studied.

DISCLOSURE OF THE INVENTION

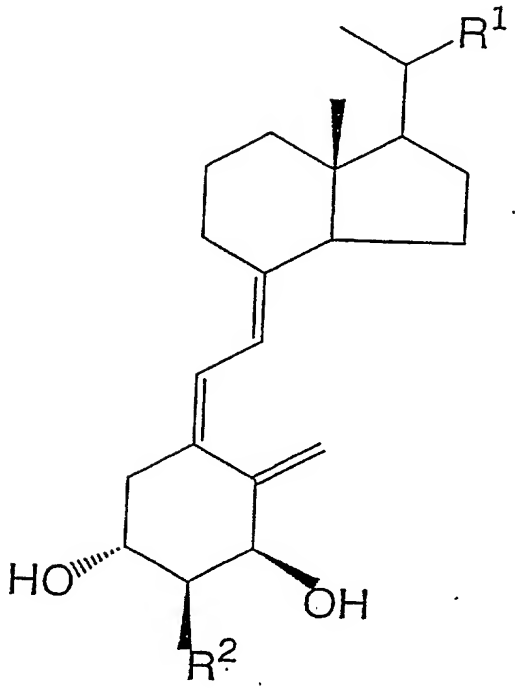
An object of the present invention is to synthesize and provide a novel vitamin D_3 derivative, in which the 2-position is substituted, other than with a methyl group, the hydroxy groups at 1- and 3-positions are α- and β-oriented, respectively, and the groups at the 20-position are epimerized.

Another object of the present invention is to evaluate bioavailability of the synthesized vitamin D_3 derivative.

As a result of careful studies to achieve the above objects, the inventors of the present invention have succeeded in synthesizing vitamin D derivatives having a variety of configurations by synthesizing CD-ring compounds each having a desired side chain portion and then coupling it with A-ring compounds each having a desired group at the 2α-position, thereby completing the present invention.

According to an aspect of the present invention, a

vitamin D derivative represented by Formula (I) is provided:



(I)

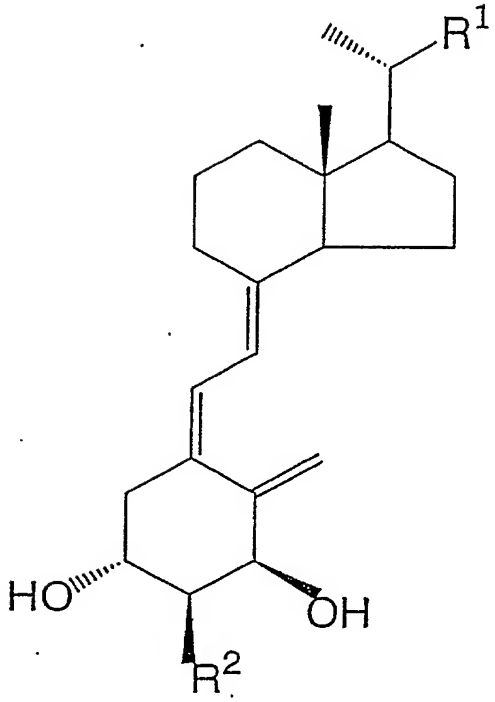
wherein

R^1 represents a saturated aliphatic C_{1-15}hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic C_{1-10}hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

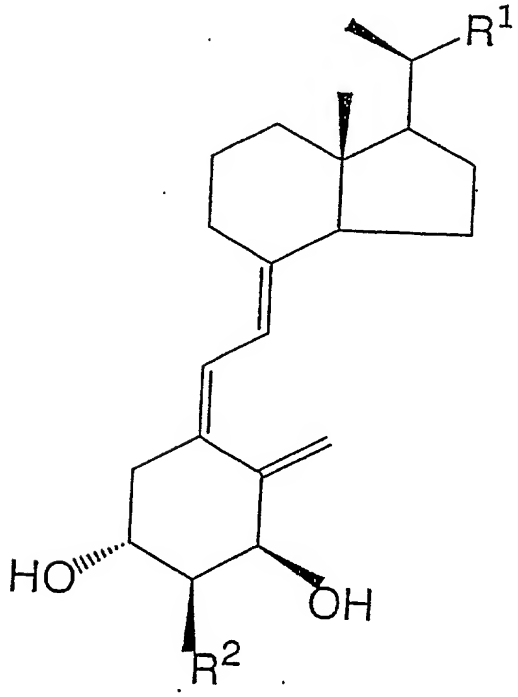
Among such vitamin D derivatives, those represented

by the following Formula (II) or



(II)

(III) are preferred.



(III)

In Formulae (I), (II) and (III), R^2 is preferably a hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethyl, propyl, butyl, pentyl or hexyl group.

In Formulae (I), (II) and (III), R^1 is preferably a saturated aliphatic $C_{1\sim15}$hydrocarbon group substituted with one hydroxy or protected hydroxy group, more preferably R^1 is a 4-hydroxy-4-methylpentyl group.

Particularly preferred compounds of the present invention are those selected from the group consisting of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-pentyl-1,3,25-triol and (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol.

According to the present invention, a pharmaceutical composition comprising the above mentioned vitamin D derivative as an active ingredient is provided. Examples of such medicaments include therapeutic agents for diseases accompanied with abnormal calcium metabolism, an antitumor agent, an immunomodulator, and the like.

According to the present invention, use of the above mentioned vitamin D derivative for a medicament is provided. Examples of such medicaments include therapeutic agents for diseases accompanied with abnormal calcium metabolism, an antitumor agent, an immunomodulator, and the like.

PREFERRED MODE FOR CARRYING OUT THE INVENTION

Detailed modes and methods with respect to vitamin D derivatives represented by Formula (I) and pharmaceutical compositions including the vitamin D derivatives in accordance with the present invention are described in further detail below.

The contents of the specification of Japanese Patent Application No.11-241650, the application on the basis of which the present application claims priority are to be incorporated in their entirety by reference.

In Formula (I), R^1 represents a saturated aliphatic C_{1-15}hydrocarbon group which may be substituted with 1 to 3 hydroxy groups or protected hydroxy groups.

In the present application, a saturated aliphatic hydrocarbon group generally means a straight or branched

alkyl group. Specific examples thereof include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, i-butyl and tert-butyl groups, and further include pentyl, hexyl, heptyl, octyl, nonyl and decanyl groups. Among them, 3-methylbutyl, 3-ethylpentyl, 4-methylpentyl, 3-(n-propyl)hexyl, 4-ethylhexyl, 5-methylhexyl, 6-methylheptyl, 5-ethylheptyl and 4-(n-propyl)hepty groups are preferred.

R^1 is preferably a 5-methylhexyl, 4-ethylhexyl or 4-methylpentyl group.

The saturated aliphatic hydrocarbon groups optionally substituted with hydroxy groups means that any hydrogen atoms in the above mentioned saturated hydrocarbon groups may be substituted with one or more hydroxy groups.

In the definition of R^1, the number of hydroxy substituents is 0, 1, 2 or 3, preferably 1 or 2, and more preferably 1. Specific examples of the saturated aliphatic hydrocarbon groups substituted with at least one hydroxy group include 2-hydroxy-2-methylpropyl, 3-hydroxy-2-methylpropyl, 2,3-dihydroxy-2-methylpropyl, 2-ethyl-2-hydroxybutyl, 2-ethyl-3-hydroxybutyl, 2-ethyl-2,3-dihydroxybutyl, 2-hydroxy-2-(n-propyl)pentyl, 3-hydroxy-2-(n-propyl)pentyl, 2,3-dihydroxy-2-(n-propyl)pentyl, 2-hydroxy-3-methylbutyl, 3-hydroxy-3-methylbutyl, 4-hydroxy-3-methylbutyl, 2,3-dihydroxy-3-methylbutyl, 2,4-dihydroxy-3-methylbutyl, 3,4-dihydroxy-3-methylbutyl, 3-ethyl-2-hydroxypentyl, 3-ethyl-3-hydroxypentyl, 3-ethyl-4-hydroxypentyl, 3-ethyl-2,3-dihydroxypentyl, 3-ethyl-2,4-dihydroxypentyl, 3-ethyl-3,4-dihydroxypentyl, 2-hydroxy-3-

(n-propyl)hexyl, 3-hydroxy-3-(n-propyl)hexyl, 4-hydroxy-3-(n-propyl)hexyl, 2,3-dihydroxy-3-(n-propyl)hexyl, 2,4-dihydroxy-3-(n-propyl)hexyl, 3,4-dihydroxy-3-(n-propyl)hexyl, 3-hydroxy-4-methylpentyl, 4-hydroxy-4-methylpentyl, 5-hydroxy-4-methylpentyl, 3,4-dihydroxy-4-methylpentyl, 3,5-dihydroxy-4-methylpentyl, 4,5-dihydroxy-4-methylpentyl, 4-ethyl-3-hydroxyhexyl, 4-ethyl-4-hydroxyhexyl, 4-ethyl-5-hydroxyhexyl, 4-ethyl-3,4-dihydroxyhexyl, 4-ethyl-3,5-dihydroxyhexyl, 4-ethyl-4,5-dihydroxyhexyl, 3-hydroxy-4-(n-propyl)heptyl, 4-hydroxy-4-(n-propyl)heptyl, 5-hydroxy-4-(n-propyl)heptyl, 3,4-dihydroxy-4-(n-propyl)heptyl, 3,5-dihydroxy-4-(n-propyl)heptyl, 4,5-dihydroxy-4-(n-propyl)heptyl, 4-hydroxy-5-methylhexyl, 5-hydroxy-5-methylhexyl, 6-hydroxy-5-methylhexyl, 4,5-dihydroxy-5-methylhexyl, 4,6-dihydroxy-5-methylhexyl, 5,6-dihydroxy-5-methylhexyl, 5-ethyl-4-hydroxyheptyl, 5-ethyl-5-hydroxyheptyl, 5-ethyl-6-hydroxyheptyl, 5-ethyl-4,5-dihydroxyheptyl, 5-ethyl-4,6-dihydroxyheptyl, 5-ethyl-5,6-dihydroxyheptyl, 4-hydroxy-5-(n-propyl)octyl, 5-hydroxy-5-(n-propyl)octyl, 6-hydroxy-5-(n-propyl)octyl, 4,5-dihydroxy-5-(n-propyl)octyl, 4,6-dihydroxy-5-(n-propyl)octyl, 5,6-dihydroxy-5-(n-propyl)octyl, 5-hydroxy-6-methylheptyl, 6-hydroxy-6-methylheptyl, 7-hydroxy-6-methylheptyl, 5,6-dihydroxy-6-methylheptyl, 5,7-dihydroxy-6-methylheptyl, 6,7-dihydroxy-6-methylheptyl, 6-ethyl-5-hydroxyoctyl, 6-ethyl-6-hydroxyoctyl, 6-ethyl-7-hydroxyoctyl, 6-ethyl-5,6-dihydroxyoctyl, 6-ethyl-5,7-dihydroxyoctyl, 6-ethyl-6,7-

dihydroxyoctyl, 5-hydroxy-6-(n-propyl)nonyl, 6-hydroxy-6-(n-propyl)nonyl, 7-hydroxy-6-(n-propyl)nonyl, 5,6-dihydroxy-6-(n-propyl)nonyl, 5,7-dihydroxy-6-(n-propyl)nonyl and 6,7-dihydroxy-6-(n-propyl) groups. Among them, 4-hydroxy-4-methylpentyl, 4-ethyl-4-hydroxyhexyl, 5-hydroxy-5-methylhexyl and 5-ethyl-5-hydroxyheptyl groups are more preferred and a 4-hydroxy-4-methylpentyl group is further more preferred.

Examples of protecting groups for the hydroxy groups in R^1 of Formulae (I), (II) and (III) include acyl groups, substituted silyl groups and substituted alkyl groups, preferably acyl groups and substituted silyl groups.

Acyl groups mean substituted carbonyl groups; examples of the substituents of the carbonyl groups include a hydrogen atom, optionally substituted lower alkyl groups, optionally substituted aryl groups, optionally substituted lower alkyloxy groups, optionally substituted aryloxy groups, optionally substituted aralkyloxy groups and the like. Preferred examples of the acyl groups include a formyl group, lower alkylcarbonyl groups, optionally substituted phenylcarbonyl groups, lower alkyloxycarbonyl groups, optionally substituted phenylalkyloxycarbonyl groups and the like, more preferred examples include formyl, acetyl, propionyl, butyryl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and benzyloxycarbonyl groups.

Substituted silyl groups mean silyl groups substituted with lower alkyl groups which may have one or

more substituents, optionally substituted aryl groups and the like. Preferably, substituted silyl groups mean tri-substituted silyl groups. Preferred examples of the substituted silyl groups include trimethylsilyl, triethylsilyl, triisopropylsilyl, tert-butyldiphenylsilyl and tert-butyldimethylsilyl groups.

Substituted alkyl groups mean those alkyl groups which are substituted with one or more substituents. Preferred examples of the substituents include optionally substituted alkyloxy groups and optionally substituted aryl groups, with optionally substituted alkyloxy groups being particularly preferred. Examples of the alkyl groups substituted with an optionally substituted alkyloxy group (such as an alkyloxy group) include, for example, methoxymethyl, 2-methoxyethoxymethyl and tetrahydropyran-2-yl groups. Examples of the substituents include halogen atoms and cyano, nitro, amino, hydroxy, alkyl, alkyloxy, acyloxy and sulfonyl groups and the like.

In Formulae (I), (II) and (III), R^2 represents a saturated aliphatic hydrocarbon group which may be substituted with one or more of substituents selected from the group consisting of a hydroxy group, halogen atoms, cyano, lower alkoxy, amino and acylamino groups.

Examples of the saturated aliphatic hydrocarbon groups include the above described straight or branched alkyl groups, preferably having 1-10 carbon atoms, more preferably 1-6 carbon atoms, and particularly preferably 3-5 carbon atoms.

The halogen atoms include fluorine, chlorine, bromine and iodine atoms, and the lower alkoxy groups mean those having 1-6 carbon atoms. The hydroxy and amino group may have protecting groups.

Similar to the above, preferred examples of the acyl groups of the acylamino group include a formyl group, lower alkylcarbonyl groups, optionally substituted phenylcarbonyl groups, lower alkyloxycarbonyl groups, optionally substituted phenylalkyloxycarbonyl groups and the like, more preferably formyl, acetyl, propionyl, butyryl, pivaloyl, benzoyl, methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl and benzyloxycarbonyl groups.

As the substituents, a hydroxy group and a halogen atom are preferred. The number of substituents is 0, 1, 2 or 3, preferably 1 or 2, and more preferably 1.

It is particularly preferred that R^2 is a hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl, hydroxyhexyl, ethyl, propyl, butyl, pentyl or hexyl group.

The stereochemstry of the hydroxy groups at the 1- and 3-positions and the methyl group at the 2-position in compounds of Formula (I) of the present invention can occur in α or β conformation, and the respective compounds are all included within the scope of the present invention.

Examples of the compounds of Formula (I) of the present invention include 1α,25-dihydroxy-2α-hydroxymethylvitamin D_3, 1α,25-dihydroxy-2α-hydroxyethylvitamin D_3, 1α,25-dihydroxy-2α-

hydroxypropylvitamin D_3, 1α,25-dihydroxy-2α-hydroxybutylvitamin D_3, 1α,25-dihydroxy-2α-hydroxypentylvitamin D_3, 1α,25-dihydroxy-2α-hydroxyhexylvitamin D_3, 1α,25-dihydroxy-2α-ethylvitamin D_3, 1α,25-dihydroxy-2α-propylvitamin D_3, 1α,25-dihydroxy-2α-butylvitamin D_3, 1α,25-dihydroxy-2α-pentylvitamin D_3 and 1α,25-dihydroxy-2α-hexylvitamin D_3. Particularly preferred examples include (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol, (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-pentyl-1,3,25-triol and (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol.

Although there is no limitation with respect to methods for synthesizing the compounds represented by Formula (I) of the present invention, for example, A-ring

and CD-ring parts of a vitamin D derivative are separately synthesized and then subjected to coupling, as described in the following Examples.

CD-ring part compounds of the vitamin D derivatives are known. A desired CD-ring compound can be obtained by appropriately modifying a side chain of a known CD-ring compound or can be obtained from a known CD-ring compound having a corresponding side chain.

These known vitamin D derivatives are disclosed in Japanese Patent Publication (Kokai) Nos. 61-267550, 6-72994 and 6-256300, Japanese Patent Publication (Kohyo) Nos. 4-503669 and 4-504573, and Japanese Patent Publication (Kokai) No. 10-182597, WO 94/14766, WO 95/27697, and the like. After protecting the hydroxy group of the above mentioned vitamin D derivative with a protecting group, the resultant compound is subjected to ozonolysis, and then, to $NaBH_4$ reduction, giving an alcohol having a hydroxy group at the 8-position. Oxidization using an appropriate oxidant gives a ketone having an oxo group at the 8-position. A CD-ring compound having a desired side chain can be obtained by converting the oxo group at the 8-position with a bromomethylene group.

A-ring compounds having a substituent at the 2β-position are known and are described by K. Konno et al. (Bioorg. Med. Chem. Lett., 8(1998) P.151-156) and T. Fujishima et al. (Bioorg. Med. Chem. Lett., 8(1998), P.2145-2148).

A-ring compounds having a substituent at the 2α-

position can be synthesized from a starting material, such as 1,2-O-isopropylidene-α-D-(R)-xylofuranose, according to the process described in the following Examples, however there is no limitation with respect to a method for synthesizing the compounds. Compounds other than those described in the following Examples can also be synthesized in the same manner by using corresponding starting materials.

Coupling of an A-ring compound with a CD-ring compound can be carried out using a known method. An A-ring compound, which is obtainable by the above method and which has a triple bond at one terminal and a double bond at the other terminal, is reacted with a CD-ring compound, which has a bromomethylene group at the coupling site for the A-ring compound, in the presence of a palladium catalyst such as $Pd_2(dba)_3$ and triphenylphosphine (PPh_3) in an appropriate solvent.

After the coupling reaction, the resulting product is purified in a usual manner such as thin layer chromatography and subjected to removal of the hydroxy protecting group, to give a desired vitamin D derivative having a substituent at the 2α-position.

The compounds of the present invention are preferably formulated into appropriate dosage forms with pharmaceutically acceptable carriers, excipients, disintegrants, lubricants, binders, flavors, colorants and the like; examples of the dosage forms include tablets, granules, fine granules, capsules, powders, injections,

solutions, suspensions, emulsions, percutaneous administration formulations, suppositories and the like.

There is no restriction on routes of administration for the compounds of the present invention; the compounds may be administered orally or parenterally (intravenously, intramuscularly, intraperitoneally, percutaneously and the like).

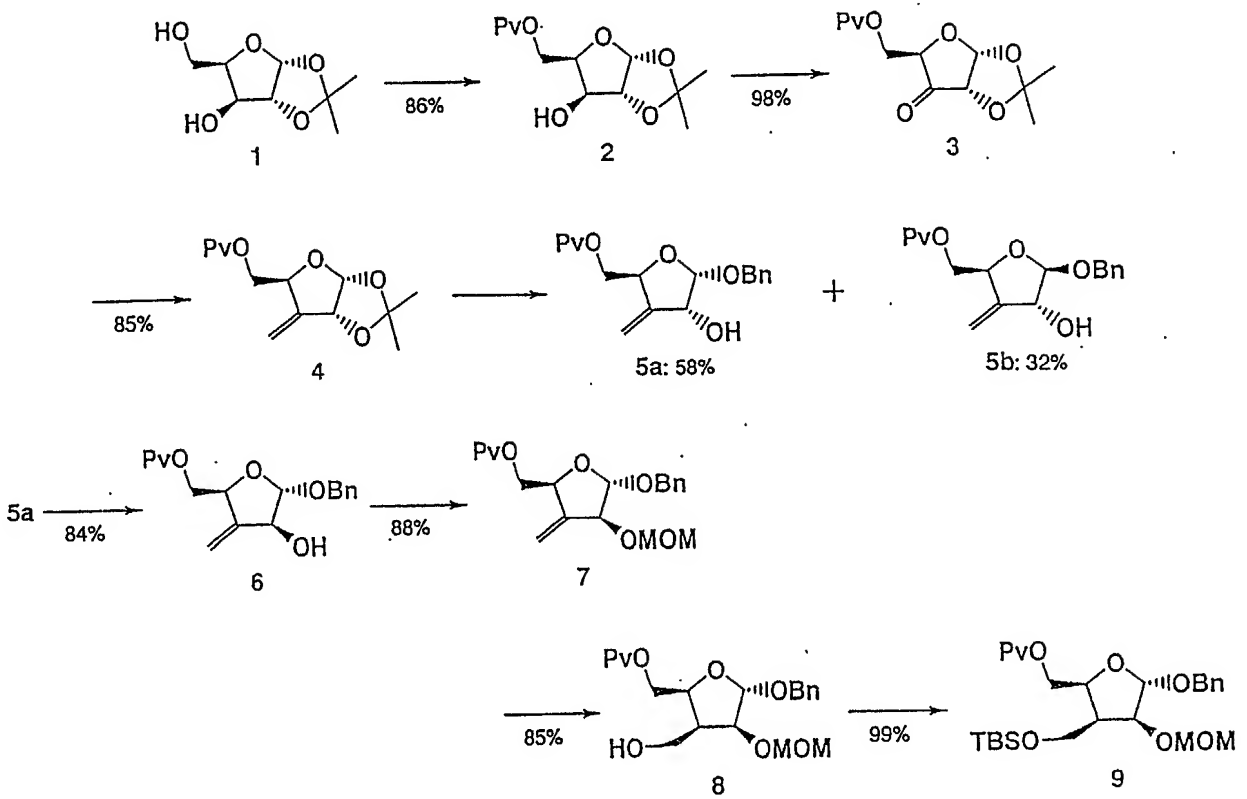
Dosage of compounds of the present invention can be appropriately chosen depending on target disease, conditions, body type, constitution, age and sex of the patient, administration route, dosage form and other factors. Typically, the lower limit for an adult ranges from 0.001 μg to 0.1 μg and preferably around 0.01 μg daily, and the upper limit for an adult ranges from 100μg to 10000 μg and preferably from 200 μg to 1000 μg daily, which may be administered at a time or in divided portions twice or three times a day.

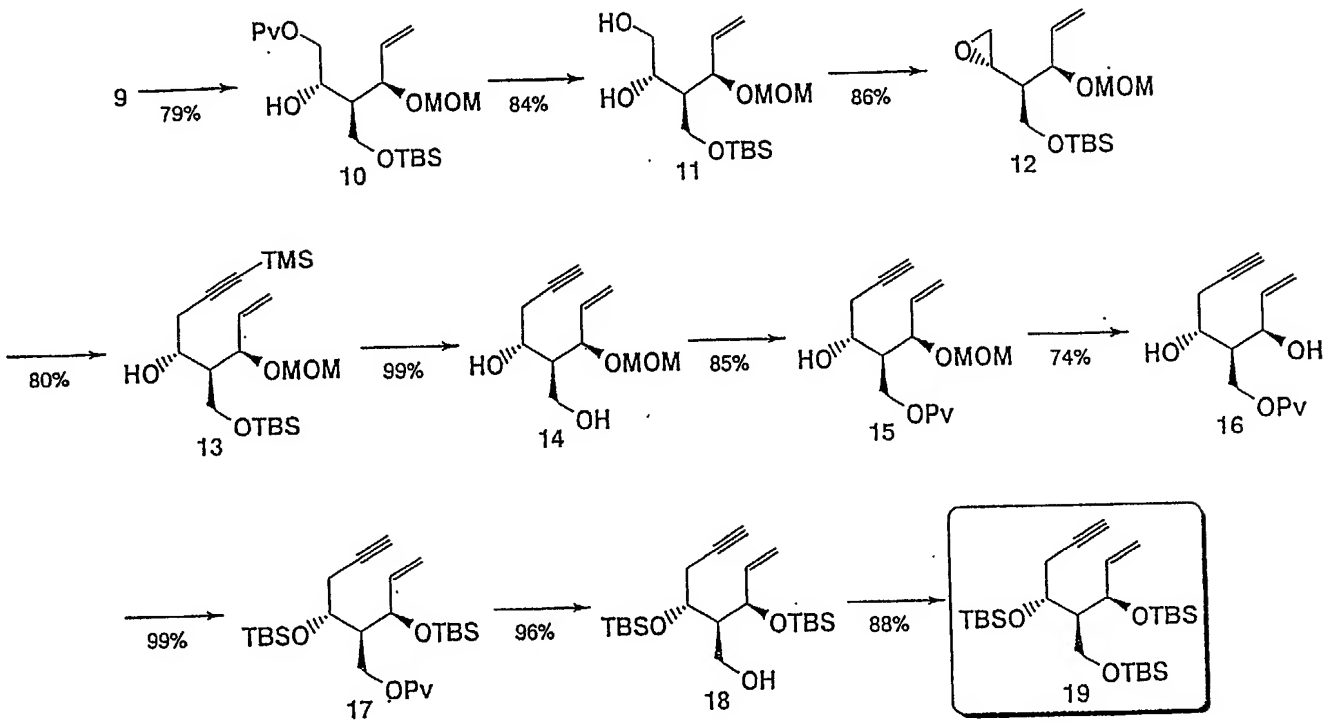
EXAMPLES

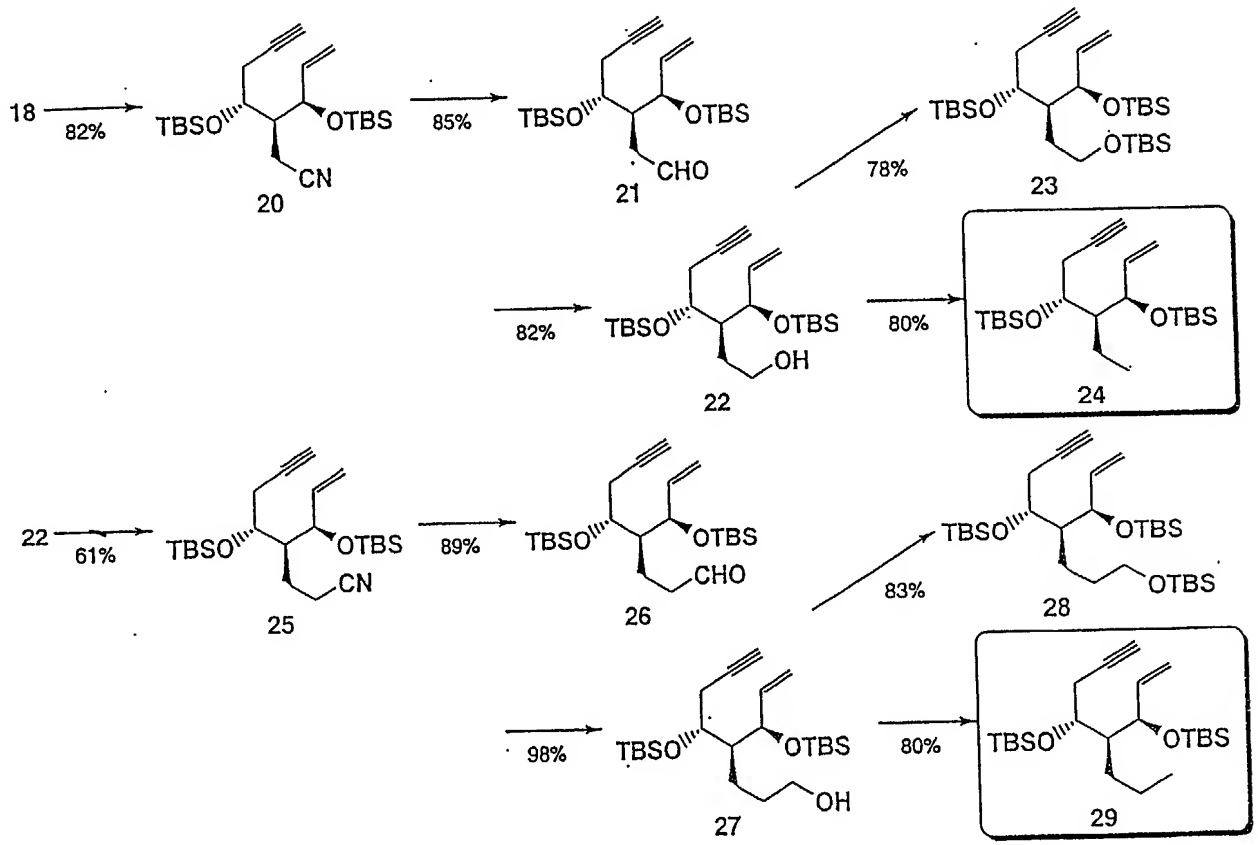
The present invention will be described specifically by way of the following Examples, which in no way limit the invention.

(Example 1): Synthesis of an A-ring compound used for the synthesis of a vitamin D derivative having a substituent at the 2α-position.

Example 1 was conducted according to the following reaction scheme:


HO
HO
1
86%
PvO
HO
2
98%
PvO
O
3
85%
PvO
4
PvO
OBn
OH
5a: 58%
+
PvO
OBn
OH
5b: 32%
5a
84%
PvO
OBn
OH
6
88%
PvO
OBn
OMOM
7
85%
PvO
OBn
HO
OMOM
8
99%
PvO
OBn
TBSO
OMOM
9


9
79%
PvO
HO
OMOM
OTBS
10
84%
HO
HO
OMOM
OTBS
11
86%
O
OMOM
OTBS
12
80%
TMS
HO
OMOM
OTBS
13
99%
HO
OMOM
OH
14
85%
HO
OMOM
OPv
15
74%
HO
OH
OPv
16
99%
TBSO
OTBS
OPv
17
96%
TBSO
OTBS
OH
18
88%
TBSO
OTBS
OTBS
19


18
82%
TBSO
OTBS
CN
20
85%
CHO
21
78%
23
82%
OH
22
80%
24
22
61%
25
89%
26
83%
28
98%
27
80%
29

(1) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene-α-D-xylofuranose (Compound 2)

1,2-O-isopropylidene-α-D-xylofuranose (Compound 1, 15.0 g, 78.9 mmol) was dissolved in pyridine (70 mL), cooled to 0°C under argon atmosphere, and trimethylacetyl chloride (9.9 g, 82.2 mmol) was added dropwise over 2 hours. The reaction mixture was stirred for 10 hours at that temperature, then MeOH (5 ml) was added and the mixture was concentrated. The residue was dissolved in diethyl ether (500 mL) and washed with water (100 mL), saturated aqueous copper sulfate solution (100 mL), water (100 mL) and saturated brine (100 mL). The aqueous layer was extracted with 100 mL of diethyl ether three times. The ether layers were combined with the previously obtained diethyl ether layer. The ether layer thus obtained was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:4) to give Compound 2 (18.7 g, 86%) as a colorless oil.

$[\alpha]^{20}_{D}$ 2.69 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 1.32 (s, 3H), 1.51 (s, 3H), 4.10 (d, 1H, J = 2.8 Hz), 3.78 (bs, 1H), 4.17 (dd, 1H, J= 5.6, 11.2 Hz), 4.25 (ddd, 1H, J= 2.8, 5.6, 7.2 Hz), 4.50 (dd, 1H, J= 7.2, 11.2 Hz), 4.56 (d, 1H, J= 3.6 Hz), 5.93 (d, 1H, J= 3.6 Hz); HREIMS $C_{12}H_{19}O_6$ (M^+-CH_3) calcd. 259.1182, found 259.1182.

(2) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene-α-D-erythro-3-pentofuranose (Compound 3)

Compound 2 (10.5 g, 38.3 mmol) was dissolved in

dichloromethane (800 mL), zeolite (75 g) and PCC (pyridinium chlorochromate) (36.5 g, 169.4 mmol) were added at room temperature and the mixture was stirred for 3 hours. The reaction mixture was diluted with hexane (800 mL), filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 2:3) to give ketone Compound 3 (10.2 g, 98%) as a colorless oil. $[\alpha]^{20}_{D}$ 4.19 (c 1.13, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.44 (s, 3H), 1.48 (s, 3H), 4.23 (d, 1H, J = 3.2, 11.6 Hz), 4.37 (dd, 1H, J= 1.2, 3.2 Hz), 4.39 (dd, 1H, J= 3.2, 11.6 Hz), 4.57 (dt, 1H, J= 1.2, 3.2 Hz), 6.10 (d, 1H, J= 4.4 Hz); HREIMS $C_{13}H_{20}O_6$ (M^+) calcd. 276.1260, found 276.1262.

(3) Synthesis of 5-O-pivaloyl-1,2-O-isopropylidene-3-deoxy-3-C-methylene-α-D-xylo-pentofuranose (Compound 4)

Methyltriphenylphosphonium bromide (7.7 g, 21.6 mmol) was mixed with THF (100 mL), and 1.0M NaHMDS (sodium bis(trimethylsilyl)amide) in THF (18.0 mL, 18.0 mmol) was added dropwise at room temperature. The yellow reaction suspension was stirred for 1.5 hours at room temperature, cooled to -78°C under argon atmosphere, and Compound 3 (4.3 g, 15.8 mmol) was slowly added. The reaction mixture was stirred at that temperature for 30 min., then warmed to room temperature and stirred for further 1 hour. The reaction mixture was cooled to 0°C, then MeOH (10 mL) was added. The mixture was diluted with diethyl ether (200 mL), and washed with a saturated aqueous ammonium chloride solution (100 mL) and with saturated brine (100 mL), each

three times. The aqueous layer was extracted with 100 mL of diethyl ether three times and combined with the previously obtained ether layer. The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give olefin Compound 4 (3.6 g, 85%) as a colorless oil.

$[\alpha]^{20}_{D}$ 13.45 (c 1.31, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.39 (s, 3H), 1.52 (s, 3H), 4.19 (dd, 1H, J = 4.8, 12.0 Hz), 4.23 (dd, 1H, J= 3.6, 12.0 Hz), 4.91 (dd, 1H, J= 1.2, 4.0 Hz), 4.94 (td, 1H, J= 2.6, 3.4, 4.8 Hz), 5.22 (t, 1H, J= 1.2 Hz), 5.48 (dd, 1H, J= 1.2, 2.4 Hz), 5.87 (d, 1H, J= 4.0 Hz); HREIMS $C_{13}H_{19}O_5$ (M^+-Me) calcd. 255.1235, found 255.1232.

(4) Synthesis of benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene-α-D-xylo-pentofuranose (Compound 5a) and benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene-β-D-xylo-pentofuranose (Compound 5b)

Compound 4 (3.2 g, 11.9 mmol) and benzyl alcohol (8.0 g, 74.1 mmol) were dissolved in toluene (22 mL), cooled to 0°C, and 4.0M hydrogen chloride-dioxane solution (10 mL, 40.0 mmol) was added. The reaction mixture was warmed to room temperature, stirred for 16 hours and diluted with a diethyl ether (200 mL). The diluted solution was cooled to 0°C and neutralized with saturated aqueous sodium bicarbonate solution (100 mL). The organic layer was washed with water (50 mL) and with saturated brine (50 mL) each three times. The aqueous layer was extracted with

50 mL of diethyl ether three times, combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give Compound 5a (2.2 g, 58%) and Compound 5b (1.22 g, 32%) as colorless oily alcohols. 5a: $[\alpha]^{20}_{D}$ 19.56 (c 1.23, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 2.26 (d, 1H, J= 11.6 Hz), 4.18 (dd, 1H, J = 4.8, 12.0 Hz), 4.60 (d, 1H, J= 12.0 Hz), 4.73 (ddt, 1H, J= 2.4, 3.4, 4.8 Hz), 4.81 (d, 1H, J= 12.0 Hz), 5.15 (d, 1H, J= 4.4 Hz), 5.18 (t, 1H, J= 2.4 Hz), 5.39 (t, 1H, J= 2.4 Hz), 7.34 (m, 5H). 5b: $[\alpha]^{20}_{D}$-4.00 (c 1.07, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 2.61 (bs, 1H), 4.14 (dd, 1H, J = 6.8, 12.0 Hz), 4.19 (dd, 1H, J= 4.8, 12.0 Hz), 4.42 (t, 1H, J= 1.2 Hz), 4.49 (d, 1H, J= 11.6 Hz), 4.76 (d, 1H, J= 11.6 Hz), 4.89 (qt, 1H, J= 1.2, 4.8, 6.2 Hz), 5.03 (s, 1H), 5.26 (t, 1H, J= 1.2 Hz), 7.33 (m, 5H).

(5) Synthesis of benzyl 5-O-pivaloyl-3-deoxy-3-C-methylene-α-D-xylo-pentofuranoside (Compound 6)

Compound 5a (2.0 g, 6.25 mmol), p-nitrobenzoic acid (2.1 g, 12,6 mmol) and triphenylphosphine (3. 3 g, 12.6 mmol) were dissolved in THF (40 mL), cooled to 0°C under argon atmosphere, and a 40% DEAD-toluene solution (5.8 g, 13.9 mmol) was added. The reaction mixture was stirred at that temperature for 15 min., warmed to room temperature and stirred for further 3 hours. The reaction mixture was cooled to 0°C, then MeOH (10 mL) was added. The mixture was diluted with diethyl ether (100 mL) and washed with

saturated aqueous sodium bicarbonate solution (50 mL) and saturated brine (50 mL), each three times. The aqueous layer was extracted with 50 mL of diethyl ether three times, combined with the previously obtained ether layer. The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:10) to give a crude ester compound as a colorless oil, which was subjected to the next reaction without further purification.

The ester was dissolved in MeOH (100 mL), cooled to 0°C, and 1.0M aqueous sodium hydroxide solution (1.0 mL, 1.00 mmol) was added dropwise. The reaction mixture was stirred for 1 hour at the same temperature, neutralized by the addition of 1.0 M hydrochloric acid (1.5 mL, 1.5 mmol) and concentrated. The residue was dissolved in diethyl ether (200 mL) and washed with a saturated aqueous sodium bicarbonate solution (50 mL) and with saturated brine (50 mL) each three times. The aqueous layer was extracted with 50 mL of diethyl ether three times, combined with the previously obtained ether layer. The ether layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:5) to give alcohol Compound 6 (1.67 g, 84%) as a colorless oil.

$[\alpha]^{20}_{D}$ 11.18 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.09 (d, 1H, J= 7.6 Hz), 4.25 (dd, 1H, J= 4.8, 12.4 Hz), 4.33 (dd, 1H, J= 3.2, 12.4 Hz), 4.37 (d, 1H, J= 7.6 Hz), 4.55 (d, 1H, J= 11.6 Hz), 4.73 (ddd, 1H, J= 1.6,

3.2, 4.3 Hz), 4.74 (d, 1H, J= 11.6 Hz), 5.10 (s, 1H), 5.26 (s, 1H), 5.54 (t, 1H, J= 1.6 Hz), 7.33 (m, 5H).

(6) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-methylene-α-D-xylofuranose (Compound 7)

Compound 6 (1.0 g, 3.13 mmol) was dissolved in dichloromethane (25 mL), to which diisopropylethylamine (1.24 g, 9.61 mmol) and chloromethyl ethyl ether (1.29 g, 16.0 mmol) were added dropwise at 0°C. Tetrabutylammonium iodide (360 mg, 975 μmol) was added to the reaction mixture and then the mixture was stirred for 14 hours at room temperature in a dark. After the completion of the reaction, the reaction mixture was diluted with diethyl ether (150 mL) and washed with saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL), each three times. The organic layer was dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:9) to give Compound 7 (1.01 g, 88%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (s, 9H), 3.35 (s, 3H), 4.18 (dd, 1H, J= 6.4, 11.2 Hz), 4.22 (dd, 1H, J= 5.2, 11.2 Hz), 4.37 (s, 1H), 4.55 (d, 1H, J= 12.0 Hz), 4.60 (d, 1H, J= 6.8 Hz), 4.69 (ddd, 1H, J= 1.6, 5.2, 6.4 Hz), 4.75 (d, 1H, J= 12.0 Hz), 4.76 (d, 1H, J= 6.8 Hz), 5.21 (s, 1H), 5.36 (s, 1H), 5.46 (d, 1H, J= 1.6 Hz), 7.33 (m, 5H).

(7) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-hydroxymethyl-α-D-xylo-pentofuranose (Compound 8)

Compound 7 (2.0 g, 5.49 mmol) was dissolved in THF

(20 mL), cooled to 0°C, and a THF solution of 0.5M 9-BBN (9-borabicyclo[3,3,1]nonane) (20 mL, 10.0 mmol) was added dropwise. The reaction mixture was heated to 50°C, stirred for 3 hours and cooled to 0°C. To the mixture, 3.0M sodium hydroxide solution (6.4 mL, 19.2 mmol) and 30% hydrogen peroxide solution (12.8 mL) were added, followed by stirring vigorously for 2 hours at room temperature. The mixture was diluted with ethyl acetate (200 mL) and washed with water (50 mL), 5% aqueous sodium sulfite solution (50 mL) and with brine (50 mL), each three times. The thus obtained aqueous layer was extracted with 50 mL of diethyl ether three times. The ether layer was combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained residue was purified by silica gel chromatography (ethyl acetate/hexane 1:3) to give Compound 8 (1.78 g, 85%) as a colorless oil.

$[\alpha]^{20}_{D}$ 7.06 (c 1.70, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.34 (t, 1H, J= 6.0 Hz), 2.89 (tt, 1H, J= 6.0, 8.4 Hz), 3.37 (s, 3H), 3.86 (dt, 1H, J= 6.0, 11.2 Hz), 3.88 (ddd, 1H, J= 6.0, 8.4, 11.2 Hz), 4.19 (dd, 1H, J= 7.2, 11.6 Hz), 4.20 (d, 1H, J= 6.0 Hz), 4.23 (dd, 1H, J= 5.6, 11.6 Hz), 4.38 (dd, 1H, J= 5.6, 7.2, 8.4 Hz),4.50 (d, 1H, J= 12.0 Hz), 4.66 (s, 2H), 4.73 (d, 1H, J= 12.0 Hz), 5.15 (s, 1H), 7.34 (m, 5H).

(8) Synthesis of benzyl 5-O-pivaloyl-2-methoxymethyl-3-deoxy-3-C-(tert-butyldimethylsilyloxymethyl)-α-D-xylo-pentofuranose (Compound 9)

Compound 8 (2.97 g, 7.77 mmol) was dissolved in DMF (30 mL), to which solution imidazole (1.06 g, 15.6 mmol) and TBDMSCl (tert-butyldimethylsilyl chloride) (1.76 g, 11.7 mmol) were added at room temperature. The reaction mixture was stirred for 3 hours at room temperature, diluted with diethyl ether (200 mL) and washed with water (25 mL) and with saturated brine (25 mL), each three times. The thus obtained aqueous layer was extracted with 25 mL of diethyl ether three times. The ether layer was combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by silica gel chromatography (ethyl acetate/hexane 1:9) to give Compound 9 (3.82 g, 99%) as a colorless oil.

$[\alpha]^{20}_{D}$ 7.65 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.83 (s, 9H), 1.18 (s, 9H), 2.80 (qt, 1H, J= 4.8, 6.8, 8.8 Hz), 3.28 (s, 3H), 3.70 (dd, 1H, J= 6.8, 10.0 Hz), 3.76 (dd, 1H, J= 8.8, 10.0 Hz), 4.07 (d, 1H, J= 4.8 Hz), 4.09 (dd, 1H, J= 7.4, 12.0 Hz), 4.13 (dd, 1H, J= 4.8, 12.0 Hz), 4.69 (d, 1H, J= 12.0 Hz), 5.10 (s, 1H), 7.28 (m, 5H); HREIMS $C_{25}H_{41}O_6Si$ (M^+-OCH_3) calcd. 465.2673, found 465.2666.

(9) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-6-O-pivaloyl-hex-1-en-5-ol (Compound 10)

Compound 9 (3.98 g, 8.02 mmol) was dissolved in ethanol (40 mL), and $Pd(OH)_2$ (400 mg) was added, followed by stirring under hydrogen atmosphere for 12 hours at room

temperature for catalytic reduction. The reaction mixture was filtered through CELITE, and the filtrate was concentrated to give hemiacetal compound as a colorless oil which was subjected to the next reaction without further purification.

Methyltriphosphonium bromide (10.9 g, 30.5 mL) was dissolved in THF (50 mL), cooled to 0°C under argon atmosphere, and 1.0 M LiHMDS (lithium bis(trimethylsilyl)amide) in THF (29 mL, 29.0 mmol) was added dropwise. The mixture was stirred at room temperature for 40 min. and then cooled again to 0°C when the color of the mixture was changed to yellow, followed by the addition of a THF solution of the hemiacetal (20 mL). The reaction mixture was stirred for 40 min. at 0°C, then MeOH (5 mL) was added. The mixture was diluted with diethyl ether (300 mL) and washed with saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The organic layer was collected. The aqueous layer was extracted with 50 mL of diethyl ether three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:6) to give olefin Compound 10 (2.57 g, 79%) as a colorless oil.

$[\alpha]^{20}_{D}$-5.63 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.07 (s, 3H), 0.89 (s, 9H), 1.21 (s, 9H), 2.74 (ddt, 1H, J= 4.4, 7.2, 8.0 Hz), 3.40 (s, 3H), 3.54 (d, 1H,

J= 5.6 Hz), 3.82 (dd, 1H, J= 4.4, 10.4 Hz), 3.90 (dd, 1H, J= 4.8, 5.6, 7.2 Hz), 4.40 (t, 1H, J= 8.0 Hz), 4.58 (d, 1H, J= 6.4 Hz), 4.72 (d, 1H, J= 6.4 Hz), 5.30 (dd, 1H, J= 1.2, 16.8 Hz), 5.33 (dd, 1H, J= 1.2, 10.4 Hz), 5.70 (ddd, 1H, J= 8.0, 10.4, 16.8 Hz); HREIMS $C_{19}H_{37}O_5Si$ (M^+-OCH_3) calcd. 373.2411, found 373.2421.

(10) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-hex-1-en-5,6-diol (Compound 11)

Compound 10 (3.20 g, 7.92 mmol) was dissolved in dichloromethane (50 mL), and 1.0M DIBAL (diisobutyl aluminum hydride) in toluene (19.8 mL, 19.8 mmol) was added dropwise over 30 min. After 10 min., methanol (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were added to the reaction mixture, which was then diluted with diethyl ether (250 mL) and filtered through CELITE. The filtrate was washed with a saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The organic layer was collected. The aqueous layer was extracted with 25 mL of diethyl ether three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 2:3) to give diol Compound 11 (2.12 g, 84%) as a colorless oil.

$[\alpha]^{20}_{D}$-6.89 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.06 (s, 3H), 0.89 (s, 9H), 1.77 (ddt, 1H, J= 4.8,

6.5, 8.0 Hz), 2.67 (dd, 1H, J= 4.8, 8.4 Hz), 3.40(s, 3H), 3.52 (d, 1H, J= 6.0 Hz), 3.70 (m, 1H), 3.83 (d, 1H, J= 4.8 Hz), 4.14 (m, 1H), 4.30 (t, 1H, J= 8.0 Hz), 4.57 (d, 1H, J= 6.8 Hz), 4.71 (d, 1H, J= 6.8 Hz), 5.29 (d, 1H, J= 16.8 Hz), 5.32 (dd, 1H, J= 10.0 Hz), 5.69 (ddd, 1H, J= 8.0, 10.0, 16.8 Hz); HREIMS $C_{14}H_{29}O_4Si$ (M^+-OCH_3) calcd. 289.1835, found 289.1838.

(11) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-hex-1-en-5,6-epoxide (Compound 12)

Compound 11 (3.20 g, 11.6 mmol) was dissolved in dichloromethane (40 mL), mixed with DMAP (4-(dimethylamino)pyridine) (2.84 g, 23.4 mmol), cooled to 0°C and vigorously stirred. To the mixture, 2-mesitylenesulfonyl chloride (3.80 g, 17.4 mmol) was slowly added, followed by stirring at that temperature for 4 hours. The reaction mixture was diluted with diethyl ether (200 mL) and washed with water (25 mL) and with saturated brine (25 mL), each three times. The aqueous layer was extracted with 25 mL of diethyl ether three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated to give a sulfonate, which was used to the next step without further purification.

The sulfonate was dissolved in THF (50 mL), cooled to -78°C, 1.0 M LiHMDS in THF (2.5 mL, 2.5 mmol) was added dropwise. After stirring for 20 min. at that temperature, the mixture was warmed to 0°C and stirred for further 20

min. The reaction mixture was diluted with diethyl ether (200 mL), washed with a saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL), each three times. The aqueous layer was extracted with 25 mL of diethyl ether three time. The ether layers were combined with the previously obtained diethyl ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give epoxy Compound 12 (3.01 g, 86%) as a colorless oil.

$[\alpha]^{20}_{D}$-7.90 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.26 (dddd, 1H, J= 3.4, 4.0, 5.2, 7.2 Hz), 2.62 (dd, 1H, J= 2.8, 5.2 Hz), 2.87 (t, 1H, J= 5.2 Hz), 3.04 (td, 1H, J= 2.8, 3.4, 5.2 Hz), 3.35 (s, 3H), 3.70 (dd, 1H, J= 4.0, 10.0 Hz), 3.82 (dd, 1H, J= 5.2, 10.0 Hz), 4.31 (t, 1H, J= 7.2 Hz), 4.51 (d, 1H, J= 6.4 Hz), 4.68 (d, 1H, J= 6.4 Hz), 5.24 (d, 1H, J= 10.2 Hz), 5.25 (d, 1H, J= 17.2 Hz), 5.70 (ddd, 1H, J= 7.2, 10.0, 17.2 Hz); HREIMS $C_{14}H_{27}O_3Si$ (M^+-OCH_3) calcd. 271.1729, found 271.1732.

(12) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3-methoxymethyloxy-8-trimethylsilyl-oct-1-en-7-yn-5-ol (Compound 13)

Ethynyltrimethylsilane (3.88 g, 39.6 mmol) was dissolved in THF (100 mL), cooled to 0°C. 1.54M n-Butyl lithium-hexane (22.7 mL, 36.0 mmol) was slowly added. The mixture was stirred at that temperature for 15 min., then cooled to -78°C. A solution of Compound 12 (3.01 g, 9.97

mmol) in THF (20 mL) and boron trifluoride diethyl ether complex (1.70 g, 12.0 mmol) were added. The mixture was warmed to room temperature, stirred for 40 min., diluted with diethyl ether (300 mL) and washed with a saturated aqueous ammonium chloride solution (50 mL) and with saturated brine (50 mL), each three times. The aqueous layer was extracted with diethyl ether (50 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give enyne Compound 13 (3.20 g, 80%) as a colorless oil.

$[\alpha]^{20}{}_{D}$-7.14 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.11 (s, 9H), 0.87 (s, 9H), 1.93 (ddt, 1H, J= 4.0, 5.6, 8.0 Hz), 2.46 (dd, 1H, J= 8.0, 16.8 Hz), 2.63 (dd, 1H, J= 6.4, 16.8 Hz), 3.38 (s, 3H), 3.60 (d, 1H, J= 5.6 Hz), 3.81 (dd, 1H, J= 4.0, 10.0 Hz), 3.92 (dd, 1H, J= 5.6, 10.8 Hz), 4.21 (ddt, 1H, J= 5.6, 6.4, 8.0 Hz), 4.44 (t, 1H, J= 8.0 Hz), 4.58 (d, 1H, J= 6.4 Hz), 4.70 (d, 1H, J= 6.4 Hz), 5.28 (d, 1H, J= 17.2 Hz), 5.29 (d, 1H, J= 10.8 Hz), 5.71 (td, 1H, J= 8.0, 10.8, 17.2 Hz).

(13) Synthesis of 3S,4R,5R-4-hydroxymethyl-3-methoxymethyloxy-oct-1-en-7-yn-5-ol (Compound 14)

Compound 13 (3.20 g, 8.0 mmol) was dissolved in THF (45 mL), cooled to 0°C, and 1.0M TBAF (tetrabutylammonium fluoride) in THF (17.6 mL, 17.6 mmol) was added. The reaction mixture was warmed to room temperature, stirred for further 1 hour, diluted with ethyl acetate (200 mL) and

washed with a saturated aqueous ammonium chloride solution (25 mL) and with saturated brine (25 mL), each three times. The aqueous layer was extracted with ethyl acetate (25 mL) three times. The ethylacetate layers were combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 2:3) to give diol Compound 14 (1.69 g, 99%) as a colorless oil.

$[\alpha]^{20}_{D}$-11.15 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (ddt, 1H, J= 3.2, 4.8, 7.2 Hz), 2.05 (t, 1H, J= 2.8 Hz), 2.50 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 2.60 (bs, 1H), 2.63 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 3.32 (d, 1H, J= 4.4 Hz), 3.34 (s, 3H), 3.83 (dd, 1H, J= 4.8, 11.2 Hz), 4.00 (dd, 1H, J= 4.8, 11.2 Hz), 4.30 (ddt, 1H, J= 3.2, 4.4, 6.8 Hz), 4.44 (tt, 1H, J= 1.2, 7.2 Hz), 4.61 (d, 1H, J= 6.8 Hz), 4.70 (d, 1H, J= 6.8 Hz), 5.33 (dt, 1H, J= 1.2, 10.4 Hz), 5.35 (d, 1H, J= 1.2, 17.2 Hz), 5.71 (ddd, 1H, J=7.2, 10.4, 17.2 Hz).

(14) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-3-methoxymethyloxy-oct-1-en-7-yn-5-ol (Compound 15)

Compound 14 (1.62 g, 7.57 mmol) was dissolved in pyridine (1.7 mL) and dichloromethane (6.8 mL) and cooled to 0°C. To the solution, trimethylacetyl chloride (1.08 g, 8.96 mmol) was added dropwise over 30 min., and stirred at the same temperature for 1 hour. The reaction mixture was warmed to room temperature, stirred for 4 hours, diluted with diethyl ether (100 mL) and washed with saturated aqueous ammonium chloride solution (20 mL) and with

saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:4) to give alcohol Compound 15 (1.92 g, 85%) as a colorless oil.

$[\alpha]^{20}_{D}$-10.05 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.03 (t, 1H, J= 8.0 Hz), 2.46 (ddt, 1H, J= 2.4, 4.8, 5.6 Hz), 2.46 (ddd, 1H, J= 2.4, 7.6, 16.8 Hz), 2.58 (ddd, 1H, J= 2.4, 6.4, 16.8 Hz), 3.10 (d, 1H, J= 2.4 Hz), 3.39 (s, 3H), 4.26 (ddt, 1H, J= 2.4, 6.4, 7.6 Hz), 4.29 (dd, 1H, J= 5.6, 11.6 Hz), 4.33 (dd, 1H, J= 5.6, 11.6 Hz), 4.40 (ddt, 1H, J = 1.2, 4.8, 6.8 Hz), 4.44 (t, 1H, J= 8.0 Hz), 4.57 (d, 1H, J= 7.2 Hz), 4.70 (d, 1H, J= 7.2 Hz), 5.31 (dt, 1H, J= 1.2, 17.6 Hz), 5.34 (d, 1H, J= 1.2, 10.4 Hz), 5.71 (ddd, 1H, J= 6.8, 10.4, 17.6 Hz).

(15) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-oct-1-en-7-yn-3,5-diol (Compound 16)

Compound 15 (2.10 g, 7.05 mmol) was dissolved in tert-butyl alcohol (60 mL). Pyridinium p-toluenesulfonate (17.6 g, 70.0 mmol) was added. The mixture was refluxed for 12 hours. The reaction mixture was cooled to room temperature and then concentrated. The residue was diluted with diethyl ether (200 mL) and washed with saturated sodium bicarbonate solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The

ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:3) to give diol Compound 16 (1.33 g, 74%) as a colorless oil.

$[\alpha]^{20}_{D}$ 1.75 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 9H), 2.05 (t, 1H, J= 2.4 Hz), 2.06 (dddd, 1H, J= 2.4, 4.4, 5.6, 6.8 Hz), 2.43 (ddd, 1H, J= 2.4, 7.2, 16.8 Hz), 2.57 (ddd, 1H, J= 2.4, 7.2, 16.8 Hz), 2.73 (d, 1H, J= 4.4 Hz), 3.07 (d, 1H, J= 2.4 Hz), 4.24 (tt, 1H, J= 2.4, 7.2 Hz), 4.31 (dd, 1H, J= 5.6, 11.6 Hz), 4.43 (dd, 1H, J= 6.8, 11.6 Hz), 4.45 (ddt, 1H, J= 1.2, 4.4, 5.6 Hz), 5.28 (dt, 1H, J= 1.2, 10.4 Hz), 5.28 (dt, 1H, J= 1.2, 10.4 Hz), 5.40 (d, 1H, J= 1.2, 16.8 Hz), 5.92 (ddd, 1H, J= 5.6, 10.4, 16.8 Hz).

(16) Synthesis of 3S,4R,5R-4-pivaloyloxymethyl-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 17)

Compound 16 (1.31 g, 5.16 mmol) was dissolved in dichloromethane (25 mL), cooled to 0°C, and 2,6-lutidine (2.21 g, 20.6 mmol) and TBDMSOTf (tert-butyldimethylsilyltriflate) (4.09 g, 15.5 mmol) were added. The reaction mixture was stirred for 2 hours at the same temperature, diluted with diethyl ether (150 mL) and washed with a saturated aqueous sodium bicarbonate solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium

sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:40) to give silyl ether Compound 17 (2.47 g, 99%) as a colorless oil.

$[\alpha]^{20}{}_{D}$-0.37 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 1.20 (s, 9H), 1.98 (t, 1H, J= 2.4 Hz), 2.19 (dq, 1H, J= 4.0, 6.0 Hz), 2.45 (ddd, 1H, J= 2.4, 4.8, 16.4 Hz), 2.54 (ddd, 1H, J= 2.4, 7.2, 16.4 Hz), 3.99 (dd, 1H, J= 6.0, 12.0 Hz), 4.16 (ddd, 1H, J= 4.0, 4.8, 7.2 Hz), 4.17 (dd, 1H, J = 6.0, 7.6 Hz), 4.25 (dd, 1H, J= 6.0, 12.0 Hz), 5.09 (d, 1H, J= 10.0 Hz), 5.16 (d, 1H, J = 17.2 Hz), 5.84 (ddd, 1H, J= 7.6, 10.0, 17.2 Hz); HREIMS $C_{22}H_{41}O_4Si_2$ (M^+-t-Bu) calcd. 425.2543, found 425.2543

(17) Synthesis of 3S,4R,5R-4-hydroxymethyl-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 18)

Compound 17 (2.47 g, 5.12 mmol) was dissolved in dichloromethane (20 mL) and cooled to -78°C. 1.0M Diisobutyl aluminium hydride in toluene (7.7 mL, 7.70 mmol) was added dropwise over 30 min. The mixture was stirred at the same temperature for 10 min. Methanol (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were added, and diluted with diethyl ether (200 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (20 mL) and with saturated brine (20 mL), each three times. The aqueous layer was extracted with diethyl ether (20 mL) three times. The ether layers were combined with the

previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:10) to give alcohol Compound 18 (1.96 g, 96%) as a colorless oil.

$[\alpha]^{20}_{D}$ 0.11 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.10 (s, 3H), 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 18H), 2.01 (t, 1H, J= 2.8 Hz), 2.09 (ddt, 1H, J= 2.0, 4.8, 7.2 Hz), 2.46 (ddd, 1H, J= 2.8, 4.8, 16.8 Hz), 2.51 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 3.07 (dd, 1H, J= 4.8, 7.2 Hz), 3.72 (ddd, 1H, J= 4.8, 7.2, 12.4 Hz), 3.82 (dt, 1H, J = 7.2, 12.4 Hz), 4.08 (dt, 1H, J= 4.8, 6.8 Hz), 4.33 (dd, 1H, J= 6.0, 12.0 Hz), 5.20 (dt, 1H, J = 2.0, 10.4 Hz), 5.28 (dt, 1H, J = 2.0, 17.2 Hz), 5.84 (ddd, 1H, J= 7.2, 10.4, 17.2 Hz); HREIMS $C_{21}H_{42}O_3Si_2$ (M^+) calcd. 398.2672, found 398.2669.

(18) Synthesis of 3S,4R,5R-4-(tert-butyldimethylsilyloxymethyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 19)

Compound 18 (40.0 mg, 101 μmol) was dissolved in DMF (2.0 mL), and imidazole (13.6 mg, 200 μmol) and TBDMSCl (tert-butyldimethylsilyl chloride) (22.6 mg, 150 μL) were added at room temperature. The mixture was stirred for 3 hours. The reaction mixture was diluted with diethyl ether (20 mL) and washed with water (5 mL) and with saturated brine (5 mL), each three times. The aqueous layer was extracted with diethyl ether (5 mL) three times. The ether layers were combined with the previously obtained ether

layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:50) to give silyl ether Compound 19 (46.0 mg, 88%) as a colorless oil. $[\alpha]^{20}_{D}$ 0.59 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.10 (s, 3H), 0.89 (s, 9H), 0.90 (s, 18H), 1.93 (t, 1H, J= 2.8 Hz), 2.00 (ddt, 1H, J= 5.2, 5.6, 6.4 Hz), 2.44 (ddd, 1H, J= 2.8, 5.6, 16.8 Hz), 2.57 (ddd, 1H, J= 2.8, 5.6, 16.8 Hz), 3.56 (dd, 1H, J= 6.0, 10.0 Hz), 3.81 (dd, 1H, J= 6.0, 10.0 Hz), 4.09 (dt, 1H, J = 4.8, 5.6 Hz), 4.30 (ddt, 1H, J= 1.2, 5.2, 6.8 Hz), 5.03 (dt, 1H, J= 1.2, 9.6 Hz), 5.11 (dt, 1H, J = 1.2, 17.2 Hz), 5.92 (ddd, 1H, J= 6.8, 9.6, 17.2 Hz).

(19) Synthesis of (3S,4R,5R-4-cyanomethyl-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 20)

Compound 18 (314 mg, 789 μmol) was dissolved in dichloromethane, and DMAP (dimethylaminopyridine) (372 mg, 3.04 mmol) was added, followed by cooling to 0°C. 2-Mesitylenesulfonyl chloride (582 mg, 2.66 mml) was added with vigorous stirring. The mixture was stirred for 12 hours at the same temperature. The reaction mixture was diluted with diethyl ether (100 mL) and washed with water (15 mL) and with saturated brine (15 mL), each three times. The aqueous layer was extracted with diethyl ether (15 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained residue was subjected to the next step without further

purification.

The sulfon ester was dissolved in DMSO (dimethylsulfoxide) (5.0 mL), and sodium cyanide (78.0 mg, 1.59 mmol) was added, followed by stirring at 70°C for 2 hours. The reaction mixture was cooled to room temperature, diluted with diethyl ether (100 mL) and washed with water (15 mL) and with saturated brine (15 mL), each three times. The aqueous layer was extracted with diethyl ether (15 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:20) to give nitrile Compound 20 (263 mg, 82%) as a colorless oil.

$[\alpha]^{20}_{D}$-0.44 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.09 (s, 3H), 0.12 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 0.91 (s, 9H), 2.03 (t, 1H, J= 2.8 Hz), 2.29 (tt, 1H, J= 6.0, 6.8 Hz), 2.36 (dd, 1H, J= 6.0, 16.4 Hz), 2.46 (ddd, 1H, J= 2.8, 4.4, 16.8 Hz), 2.48 (dd, 1H, J= 6.0, 16.4 Hz), 2.52 (ddd, 1H, J= 2.8, 6.8, 16.8 Hz), 4.04 (dt, 1H, J = 4.4, 6.8 Hz), 4.20 (ddt, 1H, J= 1.2, 6.4, 6.8 Hz), 5.24 (dt, 1H, J= 1.2, 10.4 Hz), 5.31 (dt, 1H, J = 1.2, 16.8 Hz), 5.82 (ddd, 1H, J= 6.4, 10.4, 16.8 Hz).

(20) Synthesis of 3S,4R,5R-3,5-di-(tert-butyldimethylsilyloxy)-4-(2'-ethanal)-oct-1-en-7-yne (Compound 21)

Compound 20 (184 mg, 452 μmol) was dissolved in dichloromethane (2.0 mL), cooled to -78°C, and 1.0M

diisobutyl aluminium hydride in toluene (530 μL, 530 μmol) was added over 10 min., followed by stirring for 1 hour at that temperature. Methanol (1 mL) and a saturated aqueous ammonium chloride solution (1 mL) were added to the reaction mixture, which was then diluted with diethyl ether (100 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (10 mL) and saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:20) to give aldehyde Compound 21 (157 mg, 85%) as a colorless oil.

$[\alpha]^{20}_{D}$ 0.77 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.08 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 0.89 (s, 9H), 2.04 (t, 1H, J= 2.8 Hz), 2.37 (ddd, 1H, J= 2.8, 6.0, 16.8 Hz), 2.40 (ddd, 1H, J= 2.8, 6.4, 17.2 Hz), 2.42 (ddd, 1H, J= 1.6, 7.2, 17.2 Hz), 2.44 (ddd, 1H, J= 2.8, 6.0, 16.8 Hz), 2.68 (ddd, 1H, J= 5.2, 6.4 Hz), 3.84 (dt, 1H, J = 5.2, 6.0 Hz), 4.23 (ddt, 1H, J= 1.6, 6.4, 6.8 Hz), 5.18 (dt, 1H, J= 1.6, 10.0 Hz), 5.21 (dt, 1H, J = 1.6, 16.0 Hz), 5.73 (ddd, 1H, J = 6.8, 10.0, 16.8 Hz); HREIMS $C_{22}H_{42}O_3Si_2$ (M^+) calcd. 410.2673, found 410.2667.

(21) Synthesis of 3S,4R,5R-4-(2'-hydroxyethyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 22)

Compound 21 (157 mg, 383 μmol) was dissolved in

methanol (2.0 mL), cooled to 0°C, and sodium borohydride (28.0 mg, 741 μmol) was added, followed by stirring at the same temperature for 30 min. The reaction mixture was warmed to room temperature, diluted with diethyl ether (100 mL) and washed with water (10 mL) and with saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:9) to give alcohol Compound 22 (129 mg, 82%) as a colorless oil.

$[\alpha]^{20}_{D}$ 1.40 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.10 (s, 6H), 0.90 (s, 9H), 0.91 (s, 9H), 1.67 (m, 2H), 2.03 (t, 1H, J= 2.8 Hz), 2.29 (tt, 1H, J= 6.0, 6.8 Hz), 2.36 (dd, 1H, J= 6.0, 16.4 Hz), 2.01 (t, 1H, J= 2.4 Hz), 2.04 (ddt, 1H, J= 4.8, 5.6, 7.2 Hz), 2.41 (ddd, 1H, J= 2.4, 5.6, 17.2 Hz), 2.45 (ddd, 1H, J= 2.4, 5.6, 17.2 Hz), 2.93 (bs, 1H), 3.65 (m, 2H), 3.85 (q, 1H, J = 5.6 Hz), 4.27 (ddt, 1H, J= 1.2, 4.8, 6.8 Hz), 5.18 (dt, 1H, J= 1.2, 10.8 Hz), 5.21 (dt, 1H, J = 1.2, 17.6 Hz), 5.86 (ddd, 1H, J= 6.8, 10.8, 17.6 Hz).

(22) Synthesis of 3S,4R,5R-4-(2'-tert-butyldimethylsilyloxyethyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 23)

From Compound 22 (60.0 mg, 146 μmol), silyl ether Compound 23 (59.0 mg, 78%) was obtained according to the same procedure of Compound 19.

$[\alpha]^{20}_{D}$ 0.90 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.90 (s, 3H), 0.89 (s, 27H), 1.55 (m, 2H), 1.84 (ddt, 1H, J= 3.6, 5.2, 6.4 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.36 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 2.41 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 3.57 (dt, 1H, J= 6.4, 8.4 Hz), 3.69 (dd, 1H, J= 6.4, 10.0 Hz), 4.01 (dt, 1H, J= 3.6, 6.4 Hz), 4.13 (t, 1H, J = 6.4 Hz), 5.11 (d, 1H, J= 10.4 Hz), 5.17 (d, 1H, J= 17.2 Hz), 5.82 (ddd, 1H, J= 6.4, 10.4, 17.2 Hz).

(23) Synthesis of 3S,4R,5R-3,5-di-(tert-butyldimethylsilyloxy)-4-ethyl-oct-1-en-7-yne (Compound 24)

Compound 22 (100 mg, 243μmol) was dissolved in dichloromethane (2.0 mL), and DMAP (74.0 mg, 606 μmol) was added. The mixture was cooled to 0°C. 2-Mesitylene sulfonyl chloride (106 mg, 485 μmol) was slowly added with vigorous stirring, and then stirred for 12 hours at the same temperature. The reaction mixture was diluted with diethyl ether (100 mL) and washed with water (10 mL) and with saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The thus obtained sulfon ester was subjected to the next step without further purification.

The sulfon ester was dissolved in diethyl ether (2.0 mL), cooled to 0°C. LAH (lithium aluminium hydride) (46.0 mg, 1.20 μmol) was slowly added. The mixture was stirred

at the same temperature for 1 hour and at room temperature for further 3 hours. The reaction mixture was cooled to 0°C, and ethyl acetate (1 mL) and saturated aqueous ammonium chloride solution (1 mL) were added, followed by diluting with diethyl ether (100 mL). The mixture was filtered through CELITE. The filtrate was washed with saturated aqueous ammonium chloride solution (10 mL) and saturated brine (10 mL), each three times. The aqueous layer was extracted with diethyl ether (10 mL) three times. The ether layers were combined with the previously obtained ether layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:100) to give enyne Compound 24 (77.0 mg, 80%) as a colorless oil.

$[\alpha]^{20}_{D}$ 1.95 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 18H), 0.94 (t, 3H, J= 7.6 Hz), 1.36 (m, 2H), 1.68 (ddt, 1H, J= 3.6, 5.2, 6.0 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.39 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 4.01 (dt, 1H, J= 3.6, 6.4 Hz), 4.14 (ddt, 1H, J= 1.2, 5.2, 7.2 Hz),5.08 (dt, 1H, J= 1.2, 10.4 Hz), 5.14 (dt, 1H, J= 1.2, 16.8 Hz), 5.86 (ddd, 1H, J= 7.2, 10.4, 16.8 Hz).

(24) Synthesis of 3S,4R,5R-3,5-di-(tert-butyldimethylsilyloxy)-4-(2'-cyanoethyl)-oct-1-en-7-yne (Compound 25)

From Compound 22 (129 mg, 313 μmol), nitrile Compound 25 (80.0 mg, 61%) was obtained as a colorless oil according to the same procedure of Compound 20.

$[\alpha]^{20}{}_D$ 1.40 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.05 (s, 3H), 0.08 (s, 6H), 0.10 (s, 3H), 0.90 (s, 18H), 1.73 (m, 2H), 1.96 (q, 1H, J= 6.4 Hz), 2.03 (t, 1H, J= 2.4 Hz), 2.38 (ddd, 1H, J= 2.4, 6.0, 16.8 Hz), 2.43 (ddd, 1H, J= 2.4, 4.8, 16.8 Hz), 2.50 (dt, 2H, J= 4.0, 8.4 Hz), 3.88 (dt, 1H, J= 4.8, 6.0 Hz), 4.18 (tt, 1H, J= 1.2, 6.4 Hz), 5.19 (dt, 1H, J = 1.2, 10.4 Hz), 5.25 (dt, 1H, J= 1.2, 17.2 Hz), 5.80 (ddd, 1H, J= 6.4, 10.4, 17.2 Hz) ; HREIMS $C_{23}H_{43}O_2NSi_2$ (M^+) calcd. 421.2814, found 421.2812.

(25) Synthesis of 3S,4R,5R-3,5-di-(tert-butyldimethylsilyloxy)-4-(3'-propanal)-oct-1-en-7-yne (Compound 26)

From the nitrile Compound 25 (80.0 mg, 190 μmol), aldehyde Compound 26 (71.0 mg, 89%) was obtained as a colorless oil according to the same procedure of Compound 21.

$[\alpha]^{20}{}_D$ 0.37 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.69 (m, 2H), 1.87 (ddt, 1H, J= 5.2, 5.6, 6.0 Hz), 1.87 (ddt, 1H, J= 5.2, 5.6, 6.0 Hz), 1.99 (t, 1H, J= 2.8 Hz), 2.40 (ddd, 1H, J= 2.8, 6.0, 17.2 Hz), 2.43 (ddd, 1H, J= 2.8, 6.0, 17.2 Hz), 2.57 (ddd, 1H, J= 2.0, 2.8, 6.0 Hz), 2.59 (ddd, 1H, J= 2.0, 3.2, 6.0 Hz), 3.94 (dt, 1H, J = 4.4, 6.0 Hz), 4.17 (ddt, 1H, J= 1.6, 5.6, 6.8 Hz), 5.14 (dt, 1H, J= 1.6, 10.4 Hz), 5.25 (dt, 1H, J= 1.6, 17.2 Hz), 5.80 (ddd, 1H, J= 6.8, 10.4, 17.2 Hz).

(26) Synthesis of 3S,4R,5R-4-(3'-hydroxypropyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 27)

From the aldehyde Compound 26 (71.0 mg, 167 μmol), alcohol Compound 27 (70.0 mg, 98%) was obtained as a colorless oil according to the same procedure of Compound 22.

$[\alpha]^{20}_{D}$ 1.18 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.10 (s, 3H), 0.89 (s, 18H), 1.39 (m, 2H), 1.57 (bs, 1H), 1.66 (q, 1H, J= 6.4 Hz), 1.85 (ddt, 1H, J= 4.8, 5.2, 5.6 Hz), 1.98 (t, 1H, J= 2.8 Hz), 2.39 (ddd, 1H, J= 2.8, 6.4, 16.4 Hz), 2.43 (ddd, 1H, J= 2.8, 6.4, 16.4 Hz), 3.61 (t, 2H, J= 6.4 Hz), 3.97 (dt, 1H, J= 4.8, 6.4 Hz), 4.16 (ddt, 1H, J = 1.2, 5.6, 7.2 Hz), 5.12 (dt, 1H, J= 1.2, 9.6 Hz), 5.17 (dt, 1H, J= 1.6, 16.8 Hz), 5.84 (ddd, 1H, J= 7.2, 9.6, 16.8 Hz); HREIMS $C_{23}H_{46}O_3Si_2$ (M^+) calcd. 426.2985, found 426.2977.

(27) Synthesis of 3S,4R,5R-4-(3'-tert-butyldimethylsilyloxypropyl)-3,5-di-(tert-butyldimethylsilyloxy)-oct-1-en-7-yne (Compound 28)

From the alcohol Compound 27 (60.0 mg, 141 μmol), silyl ether Compound 28 (63.0 mg, 83%) was obtained as a colorless oil according to the same procedure of Compound 23.

$[\alpha]^{20}_{D}$ 1.00 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.03 (s, 3H), 0.04 (s, 6H), 0.05 (s, 3H), 0.07 (s, 3H), 0.09 (s, 3H), 0.89 (s, 27H), 1.32 (m, 2H), 1.56 (m, 2H), 1.75 (ddt, 1H, J= 4.0, 6.4, 6.8 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.38 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 2.42 (ddd, 1H, J= 2.8, 6.4, 16.8 Hz), 3.56 (t, 2H, J= 6.8 Hz), 4.03 (dt, 1H, J= 3.6, 6.0 Hz), 4.12 (dd, 1H, J = 6.4, 7.6 Hz), 5.08 (d, 1H,

J= 10.0 Hz), 5.14 (d, 1H, J= 17.2 Hz), 5.84 (ddd, 1H, J= 7.6, 10.0, 17.2 Hz).

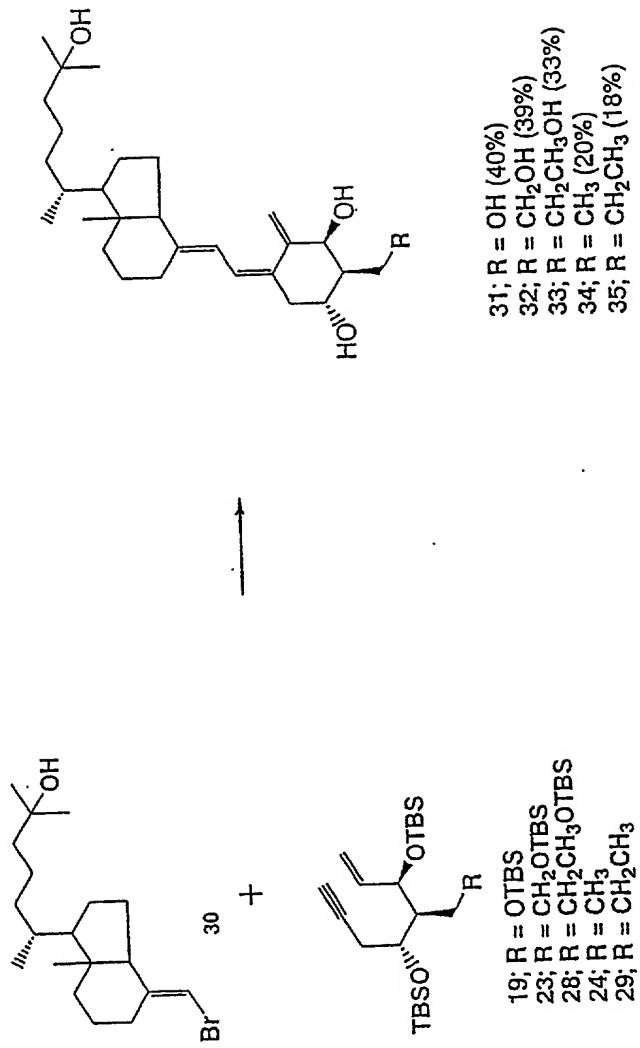
(28) Synthesis of 3S,4R,5R-3,5-di-(tert-butyldimethylsilyloxy)-4-propyl-oct-1-en-7-yne (Compound 29)

From the alcohol Compound 27 (70.0 mg, 164 μmol), enyne Compound 29 (54.0 mg, 80%) was obtained as a colorless oil according to the same procedure of Compound 24.

$[\alpha]^{20}_{D}$ 2.24 (c 1.00, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.05 (s, 6H), 0.06 (s, 3H), 0.09 (s, 3H), 0.87 (t, 3H, J= 7.2 Hz), 0.89 (s, 18H), 1.27 (m, 2H), 1.36 (m, 2H), 1.76 (ddt, 1H, J= 4.0, 5.2, 6.0 Hz), 1.95 (t, 1H, J= 2.8 Hz), 2.39 (ddd, 1H, J= 2.8, 6.4, 17.6 Hz), 2.41 (ddd, 1H, J= 2.8, 6.4, 17.6 Hz), 3.99 (dt, 1H, J= 4.0, 6.4 Hz), 4.12 (ddt, 1H, J= 1.2, 6.0, 8.0 Hz), 5.07 (dt, 1H, J= 1.2, 10.4 Hz), 5.13 (dt, 1H, J= 1.2, 17.2 Hz), 5.85 (ddd, 1H, J= 8.0, 10.4, 17.2 Hz).

(Example 2) Synthesis of vitamin D derivatives having a substituent at the 2α-position.

Example 2 was done by the following reaction scheme:



(1) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol (Compound 31)

The silyl ether Compound 19 (20.0 mg, 39.1 μmol) and a vinyl bromide 30 (20.0 mg, 58.0 μmol), which corresponds to a compound of Formula (I) in which R^1 is a 4-hydroxy-4-methylpentyl group, were dissolved in triethylamine/toluene (3:1, 2.0 mL). Tris(dibenzylideneacetone)-dipalladium(0)-

chloroform addition product (4.0 mg, 3.86 μmol) and triphenylphosphine (10.0 mg, 38.1 μmol) were added. The mixture was stirred at room temperature for 15 min. and then refluxed for 2 hours. The reaction mixture was filtered through silica gel; the filtrate was concentrated and roughly purified by thin layer chromatography (ethyl acetate/hexane 1:4) to give a protected derivative as a colorless solid. The crude protected body was subjected to the next step without further purification.

The protected derivative was dissolved in methanol (2.0 mL), cooled to 0°C and (+)-10-camphorsulfonic acid (10.0 mg, 43 μmol) was added. The mixture was stirred at the same temperature for 1 hour and then returned to room temperature, followed by stirring for further 12 hours. The reaction mixture was diluted with ethyl acetate (10 mL) and washed with saturated aqueous sodium bicarbonate solution (1.0 mL) and saturated brine (1.0 mL), each three times. The aqueous layer was extracted with ethyl acetate (2 mL) three times. The ethylacetate layers were combined with the previously obtained organic layer, dried over magnesium sulfate, filtered and concentrated. The residue was purified by thin layer chromatography (ethyl acetate/hexane 1:4) to give Compound 31 (7.0 mg, 40%) as a colorless solid.

$[\alpha]^{20}_{D}$ 12.95 (c 0.0085, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.8 Hz), 2.31 (m, 2H), 2.67 (dd, 1H, J= 4.4, 12.8 Hz), 2.73 (bs, 1H), 2.84 (m, 1H), 4.01 (m, 2H), 4.24 (m, 1H), 4.47 (bs, 1H), 5.02 (d, 1H, J=

2.0 Hz), 5.30 (d, 1H, J= 2.0 Hz), 5.98 (d, 1H, J= 10.8 Hz), 6.45 (d, 1H, J= 10.8 Hz) ; HREIMS $C_{28}H_{44}O_3$ (M^+-H_2O) calcd. 428.3290, found 428.3287.

(2) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol (Compound 32)

From the silyl ether Compound 23 (25.0 mg, 47.5 μmol), Compound 32 (8.5 mg, 39%) was obtained as a colorless solid according to the same procedure of Compound 31.

$[\alpha]^{20}_D$ 13.85 (c 0.00722, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz), 2.26 (dd, 1H, J= 8.0, 12.8 Hz), 2.53 (bs, 1H), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.79 (m, 2H), 3.94 (m, 1H), 4.37 (d, 1H, J= 2.0 Hz), 5.02 (d, 1H, J= 1.2 Hz), 5.30 (bs, 1H), 6.01 (d, 1H, J= 10.8 Hz), 6.40 (d, 1H, J= 10.8 Hz) ; HREIMS $C_{29}H_{48}O_4$ (M^+) calcd. 460.3553, found 460.3557.

(3) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol(Compound 33)

From the silyl ether Compound 28 (25.0 mg, 46.3 μmol), Compound 33 (7.2 mg, 33%) was obtained as a colorless solid according to the same procedure of Compound 31.

$[\alpha]^{20}_D$ 161.29 (c 0.00186, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz), 2.25 (dd, 1H, J= 8.4, 13.2 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.70 (t, 2H, J= 5.6 Hz), 3.90 (dt, 1H, J= 4.0, 8.0

Hz), 4.38 (d, 1H, J= 3.6 Hz), 5.00 (d, 1H, J= 1.6 Hz), 5.28 (d, 1H, J= 1.6 Hz), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz).

(4) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol (Compound 34)

From the enyne Compound 24 (30.0 mg, 75.8 μmol), Compound 34 (6.8 mg, 20%) was obtained as a colorless solid according to the same procedure of Compound 31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.0 Hz), 0.95 (t, 3H, J= 7.2 Hz), 2.24 (dd, 1H, J= 8.8, 12.8 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.37 (bs, 1H), 4.99 (d, 1H, J= 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz); HREIMS $C_{29}H_{48}O_3$ (M^+) calcd. 444.3603, found 460.3604.

(5) Synthesis of (5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol (Compound 35)

From the enyne Compound 29 (30.0 mg, 73.2 μmol), Compound 35 (6.2 mg, 18%) was obtained as a colorless solid according to the same procedure of Compound 31.

^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (s, 3H), 0.94 (d, 3H, J= 6.4 Hz),1.01 (t, 3H, J= 6.8 Hz), 2.24 (dd, 1H, J= 8.8, 12.4 Hz), 2.66 (dd, 1H, J= 4.0, 13.2 Hz), 2.83 (m, 1H), 3.89 (m, 1H), 4.39 (bs, 1H), 4.99 (d, 1H, J= 1.6 Hz), 5.27 (bs, 1H), 6.00 (d, 1H, J= 11.2 Hz), 6.40 (d, 1H, J= 11.2 Hz). ; HREIMS $C_{30}H_{50}O_3$ (M^+) calcd. 458.3760, found 458.3755.

(Test example 1) Assay for binding to vitamin D receptor (VDR)

Bovine thymus 1α,25-dihydroxyvitamin D_3 receptor was purchased from YAMASA SHOYU KABUSHIKI KAISHA (lot.110431) and 1 ampule (approximately 25 mg) of the receptor was dissolved in 55 mL of 0.05 M phosphate 0.5M potassium buffer (pH 7.4) just before use. Ethanol solutions (50 μl) of 1α,25-dihydroxyvitamin D_3 and Compounds 31-35 of the present invention at various concentrations were prepared, mixed with aliquots (500 μl, 0.23 mg protein) of the receptor solution and pre-incubated at room temperature for 1 hour. To the resultant mixtures, [^{3}H]-1α,25-dihydroxyvitamin D_3 was added at the final concentration of 0.1 nM, followed by incubation overnight at 4°C.

The reaction mixtures were treated with dextran coated charcoal for 30 minutes at 4°C to separate the bound and free forms of [^{3}H]-1α,25-dihydroxyvitamin D_3, and centrifuged at 3000 rpm for ten minutes. Each of the resultant supernatants (500 μl) was mixed with ACS-II (9.5 ml) (AMERSHAM, England) for radioactivity measurement.

The binding properties of Compounds 31-35 of the present invention were expressed in relative values with that of 1α,25-dihydroxyvitamin D_3 taken as 100. The results are shown in Table 1.

Table 1

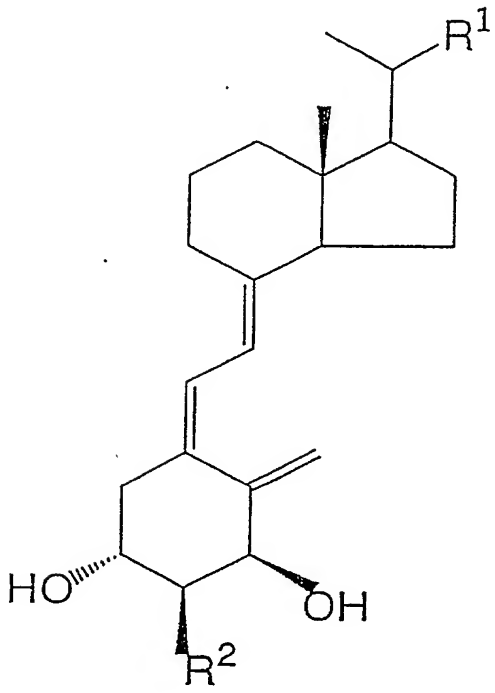
Compound	Binding property
31	20
32	70
33	300
34	40
35	20

INDUSTRIAL APPLICABILITY

Vitamin D_3 derivatives represented by Formula (I), (II) and (III) of the present invention are novel compounds and may be useful as pharmaceutical agents. The compounds of the present invention may be useful as reagents for studying metabolism of active vitamin D_3, that is, 1α,25-dihydroxyvitamin D_3.

CLAIMS

1. A vitamin D derivative represented by Formula (I):



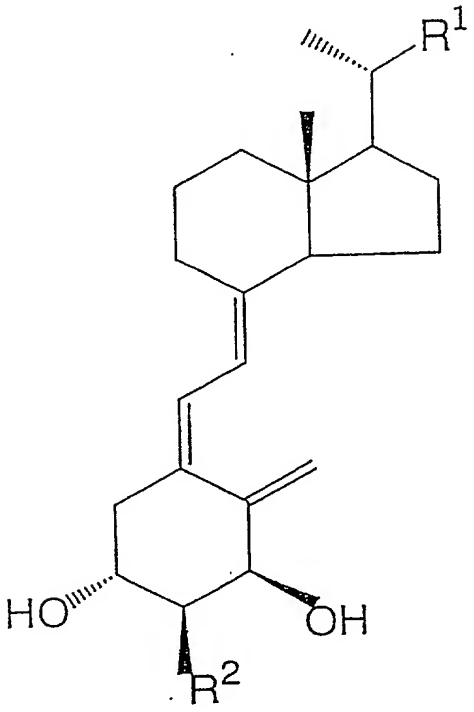
(I)

wherein

R^1 represents a saturated aliphatic C_{1-15}hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic C_{1-10}hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

2. The vitamin D derivative of claim 1 which is represented by Formula (II):



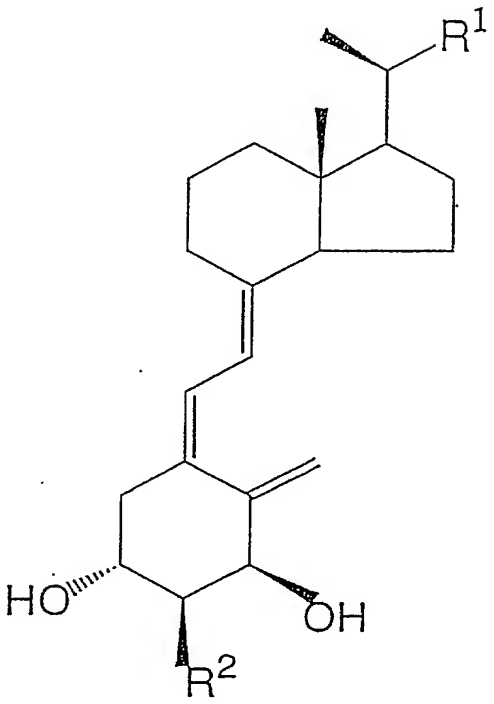
(II)

wherein

R^1 represents a saturated aliphatic C_{1-15}hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic C_{1-10}hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

3. The vitamin D derivative of claim 1 which is represented by Formula (III):



(III)

wherein

R^1 represents a saturated aliphatic $C_{1\sim15}$hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic $C_{1\sim10}$hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

4. The vitamin D derivative according to one of claims 1

to 3, wherein R^2 is a hydroxymethyl group, a hydroxyethyl group, a hydroxypropyl group, a hydroxybutyl group, a hydroxypentyl group, a hydroxyhexyl group, an ethyl group, a propyl group, a butyl group, a pentyl group or a hexyl group.

5. The vitamin D derivative according to one of claims 1 to 4, wherein R^1 is a 4-hydroxy-4-methylpentyl group.

6. The vitamin D derivative according to claim 1 selected from the group consisting of

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hydroxymethyl-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(2'-hydroxyethyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(3'-hydroxypropyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(4'-hydroxybutyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(5'-hydroxypentyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-(6'-hydroxyhexyl)-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-ethyl-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-propyl-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-butyl-1,3,25-triol,

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-

2-pentyl-1,3,25-triol and

(5Z,7E)-(1S,2S,3R,20R)-9,10-seco-5,7,10(19)-cholestatriene-2-hexyl-1,3,25-triol.

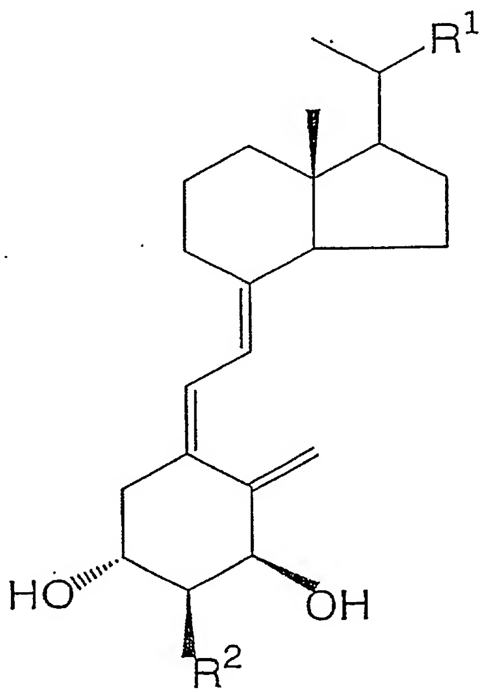
7. A pharmaceutical composition comprising a vitamin D derivative according to any one of claims 1 to 6 as an active ingredient.

8. The pharmaceutical composition according to claim 7, wherein the composition is a therapeutic agent for a disease associated with abnormal calcium metabolism, an antitumor agent or an immunomodulator.

ABSTRACT

An object of the present invention is to synthesize a novel vitamin D_3 derivative having a substituent at the 2α-position.

The present invention provides vitamin D derivatives represented by Formula (I):



(I)

wherein

R^1 represents a saturated aliphatic $C_{1\sim15}$hydrocarbon group optionally substituted with 1 to 3 hydroxy or protected hydroxy groups; and

R^2 represents a saturated aliphatic $C_{1\sim10}$hydrocarbon group optionally substituted with one or more substituents, which may be the same or different and which are selected from the group consisting of a hydroxy group, a halogen atom, a

cyano group, a lower alkoxy group, an amino group and an acylamino group, provided that when R^2 represents a saturated aliphatic C_1hydrocarbon group, R^2 is substituted with at least one substituent.

Page 1 of 2 Pages [X] Original [ ] Supplemental Atty. Docket:

Combined Declaration for Patent Application and Power of Attorney

As a below-named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and that I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

2α-SUBSTITUTED VITAMIN D DERIVATIVES

the specification of which (check one)

[ ] is attached hereto;

[ ] was filed in the United States under 35 U.S.C. §111 on _____, as U.S. Appln. No. _____*; or

[X] was/will be filed in the U.S. under 35 U.S.C. §371 by entry into the U.S. national stage of an international (PCT) application PCT/JP00/05743 filed Aug. 25, 2000, entry requested on _____*; national stage application received U.S. Appln. No. _____*; §371/§102(e) date _____* (* if known)

and was amended on _____ (if applicable).

(include dates of amendments under PCT Art. 19 and 34 if PCT)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above; and I acknowledge the duty to disclose to the Patent and Trademark Office (PTO) all information known by me to be material to patentability as defined in 37 C.F.R. §1.56.

I hereby claim foreign priority benefits under 35 U.S.C. §§ 119 and 365 of any prior foreign application(s) for patent or inventor's certificate, or prior PCT application(s) designating a country other than the U.S., listed below with the "Yes" box checked and have also identified below any such application having a filing date before that of the application on which priority is claimed:

(Number)	(Country)	(Day Month Year Filed)	YES	NO
241650/1999	Japan	27/8/1999	[X]	[ ]
			[ ]	[ ]

I hereby claim the benefit under 35 U.S.C. §120 of any prior U.S. non-provisional application(s) or prior PCT application(s) designating the U.S. listed below, or under §119(e) of any prior U.S. provisional applications listed below, and, insofar as the subject matter of each of the claims of this application is not disclosed in such U.S. or PCT application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose to the PTO all information as defined in 37 C.F.R. §1.56(a) which occurred between the filing date of the prior application and the national filing date of this application:

(Application No.)	(Day Month Year Filed)	(Status: patented, pending, abandoned)

As a named inventor, I hereby appoint the following registered practioners to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

All of the practioners associated with Customer Number 001444

Direct all correspondence to the address associated with **Customer Number 001444**; i.e.,

BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, D.C. 20001-5303
(202) 628-5197

The undersigned hereby authorizes the U.S. Attorneys or Agents appointed herein to accept and follow instructions from YUASA AND HARA as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. Attorneys or Agents and the undersigned. In the event of a change of the persons from whom instructions may be taken, the U.S. Attorneys or Agents appointed herein will be so notified by the undersigned.

Atty. Docket:

Title: 2α-SUBSTITUTED VITAMIN D DERIVATIVES

U.S. Application filed _____, Serial No. _____

PCT Application filed August 25, 2000, Serial No. PCT/JP00/05743

I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. §1001 and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Hiroaki Takayama

FULL NAME OF FIRST INVENTOR	INVENTOR'S SIGNATURE	DATE
Hiroaki TAKAYAMA 10/31/2001 HT	Hiroaki Takayama	Oct.31,2001
RESIDENT: Tokyo, Japan JPX		CITIZENSHIP: Japanese
POST OFFICE ADDRESS: 2-6-12, Hatagaya, Shibuya-ku, Tokyo 151-0072 Japan		

FULL NAME OF SECOND JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Toshie FUJISHIMA	Toshie Fujishima	Oct.31,2001
RESIDENT: Tokyo, Japan JPX		CITIZENSHIP: Japanese
POST OFFICE ADDRESS: 321-2-201, Higashiasakawa-machi, Hachioji-shi, Tokyo 193-0834 Japan		

FULL NAME OF THIRD JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Yoshitomo SUHARA	Yoshitomo Suhara	Oct.31,2001
RESIDENT: Kanagawa, Japan JPX		CITIZENSHIP: Japanese
POST OFFICE ADDRESS: 5-7-301, 1258, Tokaichiba-cho, Midori-ku, Yokohama-shi, Kanagawa 226-0025 Japan		

FULL NAME OF FOURTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Ken-ichi NIHEI	Kenichi Nihei	Oct.31,2001
RESIDENT: Kanagawa, Japan JPX		CITIZENSHIP: Japanese
POST OFFICE ADDRESS: 3-5-12-A103, Kubosawa, Shiroyama-machi, Tsukui-gun, Kanagawa 220-0105 Japan		

FULL NAME OF FIFTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
Katsuhiro KONNO	Katsuhiro Konno	Oct.31,2001
RESIDENT: Kanagawa, Japan JPX		CITIZENSHIP: Japanese
POST OFFICE ADDRESS: 1245-18, Chigira, Sagamiko-machi, Tsukui-gun, Kanagawa 199-0104 Japan		

FULL NAME OF SIXTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENT		CITIZENSHIP
POST OFFICE ADDRESS		

FULL NAME OF SEVENTH JOINT INVENTOR	INVENTOR'S SIGNATURE	DATE
RESIDENT		CITIZENSHIP
POST OFFICE ADDRESS		

ALL INVENTORS MUST REVIEW APPLICATION AND DECLARATION BEFORE SIGNING. ALL ALTERATIONS MUST BE INITIALED AND DATED BY ALL INVENTORS PRIOR TO EXECUTION. NO ALTERATIONS CAN BE MADE AFTER THE DECLARATION IS SIGNED. ALL PAGES OF DECLARATION MUST BE SEEN BY ALL INVENTORS.